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# LES CAHIERS DE L'INSTITUT DE LA VIE

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PHYSIQUE THÉORIQUE ET BIOLOGIE  
Versailles 26-30 juin 1967

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Les rapports et les discussions de la Conférence Internationale de Physique Théorique et Biologie, tenue à Versailles du 26 au 30 juin 1967, sont publiés dans les numéros 11 à 19 des Cahiers de l'Institut de la Vie.

Ils font d'autre part l'objet d'un ouvrage intitulé: Physique Théorique et Biologie — Theoretical Physics and Biology — publié en 1969 par la North-Holland Publishing Company, Keizersgracht 305-311, P.O.B. 3489, Amsterdam C (Pays-Bas). Par souci d'unité, nous avons respecté dans les présents cahiers, la numérotation des page de l'ouvrage.

Les langues officielles de la conférence étaient le français et l'anglais. Nous reproduisons les textes dans les langues d'expression de leurs auteurs.

## *Preface*

Une interrogation fondamentale sur la vie et le destin de l'homme, tel est l'objet premier de l'Institut de la Vie. Fidèle à sa vocation et à son style, l'Institut de la Vie a pris l'initiative d'organiser une conférence internationale de Physique théorique et de Biologie. Cette manifestation fut placée sous le patronage de Monsieur le Ministre d'État chargé de la recherche scientifique et technique et de l'Union internationale de Physique pure et appliquée.

Ouverte par le Professeur P. Grassé, Président de l'Académie des Sciences, marquée par un discours de Monsieur Maurice Schumann, Ministre d'Etat chargé de la recherche scientifique et des questions atomiques et spatiales, cette conférence fut caractérisée par :

- son thème: la vie
- les multiples disciplines confrontées: de la physique théorique à la biologie
- la très haute qualité des participants: plus de soixante dix savants, dont plusieurs Prix Nobel, appartenant à quatorze nations,
- la volonté de dialogue d'abord, de coopération ensuite, malgré la diversité des langages et des méthodes.

Au cours des huit séances réparties en quatre journées, furent traités quelques aspects des problèmes de la vie depuis les conceptions théoriques jusqu'aux mécanismes physiologiques. Les titres de ces quatre journées montrent bien l'itinéraire choisi:

- concepts théoriques: concepts quantiques en biologie, physique statistique et thermodynamique
- physicochimie de la vie: données et problèmes: molécules biologiques et effets quantiques, aspects biochimiques
- l'information en biologie: information et codes, les structures formelles et la symétrie
- mécanismes physiologiques: régulations, rythmes biologiques.

Pour tempérer la rigueur logique de ce programme, un vaste champ libre fut laissé aux discussions, après la présentation de chaque rapport et de chaque communication sollicitée. Ainsi la réunion a-t-elle atteint son premier but: l'intercommunication entre disciplines très différentes.

Une telle conférence n'est pas une manifestation isolée. Elle marque le début d'une série dont nous n'entrevoyons pas le terme. Une deuxième conférence se tiendra à Versailles du 30 juin au 4 juillet 1969. Et l'entreprise de l'Institut de

la Vie s'inscrit dans un ample dessein: conjuguer les ressources de la science contemporaine pour l'exploration d'un sujet fascinant, la vie.

Nous exprimons notre gratitude:

- aux membres du Comité Scientifique d'Organisation pour leur concours intellectuel: les Professeurs P. Auger, A. Fessard, H. Fröhlich, P. P. Grassé, A. Lichnérowicz, I. Prigogine et L. Rosenfeld ainsi qu'à tous les participants de la conférence.
- aux organismes publics et privés, aux entreprises et personnalités privées pour leur soutien matériel: le Ministère des Affaires Sociales, la Délégation Générale à la Recherche Scientifique et Technique, la Mutuelle Générale de l'Education Nationale, la Banque de France, la Banque Nationale pour le Commerce et l'Industrie, la Banque Neufelize, Schlumberger, Malet et Compagnie, la Banque Rothschild, la Banque Varin et Bernier, la Caisse des Dépôts et Consignations, la Caisse des Marchés de l'Etat, Monsieur André Chausson, les Ciments Lafarge, la Compagnie Minière, la Compagnie de Saint-Gobain, le Conseil National du Patronat Français, le Crédit Foncier, le Crédit Lyonnais, le Crédit National, la Discount Bank, la Fondation Synthesis (Eindhoven), Mademoiselle Joliot, la Société André Citroën, la Société Française des Pétroles B.P., la Société Générale, et les nombreux cotisants de l'Institut de la Vie, des plus prestigieux aux plus modestes.
- au Comité féminin d'accueil pour l'harmonie et la grâce qu'il a créées.
- à Madame P. Wissmer pour son inlassable activité.
- à Monsieur Frank de la North-Holland Publishing Company pour la conscience et le soin avec lesquels il a réalisé la présente édition.

M. MAROIS

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*Allocution de PIERRE AUGER*

Monsieur le Ministre, Messieurs les Présidents, Messieurs les Directeurs généraux, Messieurs les Professeurs, Messieurs les Elèves, Au nom du Comité d'organisation, je vous remercie vivement, Monsieur le Ministre, d'avoir bien voulu honorer de votre présence cette réunion. Nous remercions tous les participants d'avoir répondu si nombreux à notre appel et d'avoir donné à ce colloque, dès son début, un niveau scientifique très élevé. Mais il n'y a pas que la substance intellectuelle proprement dite qui compte, dans un colloque, il y a cet impondérable que l'on appelle l'atmosphère, et il me semble que vous avez créé une bonne atmosphère, — ce qui par parenthèse nous console un peu de l'évidente mauvaise volonté de l'atmosphère extérieure. Recevez à ce point de vue les excuses du Comité d'organisation, qui n'a pu faire mieux. Il faudrait peut-être organiser quelques colloques sur la physique théorique et la météorologie, et on rencontrerait d'ailleurs bien des problèmes semblables à ceux que vous traitez: systèmes à  $n$  corps, structures dynamiques; nous avons réagi collectivement par l'instauration de transports actifs entre le Congrès et le Trianon et individuellement par l'usage de membranes à perméabilité sélective.

Ces considérations sur le temps qu'il fait pourraient paraître un peu marginales, à propos d'un colloque qui traite, sous une forme assez particulière sans doute, du problème de la Vie. Oui, scientifiquement, mais non du point de vue humain, du point de vue, disons, populaire. Le public s'intéresse passionnément aux progrès de la science, il admire les succès des savants, et attend avec espoir les résultats de colloques comme celui-ci, mais disons-le franchement, il est très souvent déçu.

Aux explorateurs de la haute atmosphère et de l'espace, constructeurs de satellites, il adressera ses félicitations pour la découverte des zones de Van Allen ou du vent solaire. Mais ce n'était pas exactement cela qu'il demandait, ce qu'il aurait voulu c'est savoir quel temps il fera cet été. Aux membres de ce colloque il adressera ses félicitations pour la meilleure compréhension de la pompe à sodium, mais ce qu'il aurait voulu, c'est savoir ce qu'est la vie, ou plus modestement ce qu'est le cancer. En cela, ce public montre qu'il n'a pas oublié la magie de jadis et ses mirages séduisants où on lui promettait la jouvence, la pluie et le soleil à volonté, le plomb en or. Nous lui donnons des particules étrange, le zéro absolu (ou presque), des RNA messagers, des isotopes plus ou moins explosifs. Alors il faut lui expliquer, lui faire comprendre que c'est par cette voie complexe, détournée, inattendue et rude que ses grands problèmes seront résolus — ou peut-être que leur solution apparaîtra soudain comme inutile parce que dépassée.

Au fond cela provient en grande partie de ce que la science se présente au public comme constituée d'une multitude de spécialités: on n'est plus physicien, mais physicien nucléaire, et même physicien nucléaire basses énergies, ce terme pouvant d'ailleurs prêter à équivoque car ces basses énergies correspondent à

des potentiels cent fois supérieurs à ceux de nos lignes à très haute tension! L'idée de la science comme une mosaïque de spécialités est un cadeau, un mauvais cadeau de ce dix-neuvième siècle que Léon Daudet appelait stupide. Mon père, qui était chimiste, me racontait comment sa carrière avait été rendue difficile à l'Université à cause de son obstination à vouloir faire de la chimie, et non pas seulement de la chimie organique, et plus spécialement de la chimie organique aromatique, et plus spécialement de la chimie organique aromatique hétérocyclique. S'il avait fait un tel choix et s'y était tenu, il aurait fait partie d'un cénacle qui l'aurait poussé en avant, alors qu'il était considéré comme un traître pour s'être intéressé aux acides phosphoriques, basement inorganiques...

Alors comment voulez-vous que le public comprenne ce que font ensemble des physiciens, — pire, des physiciens théoriciens! — et des biologistes, qui pour lui sont encore soit des médecins, soit des naturalistes. Il faut dire, en passant, que la Biologie si elle a pu pénétrer dans les Facultés, n'a pas encore pu pénétrer dans l'Académie où elle ferait sans doute figure de "parvenue" ou de nouveau riche devant les titres de noblesse des valeurs traditionnelles comme l'Economie Rurale par exemple, qui possède une section entière à elle toute seule. Le public doit être informé du grand mouvement actuel de la science vers une rupture des barrières entre spécialités et même entre les disciplines générales. Il doit savoir que les grands principes, les grandes lois traversent tout le champ des sciences, qu'elles soient exactes ou naturelles, et à condition qu'elles ne soient pas inexactes ou surnaturelles. Conservation de l'énergie, du moment cinétique, croissance de l'entropie, principe de symétrie, de relativité, lois quantiques, bien d'autres encore permettent de revenir à une conception unitaire de la science, conception qui avait été celle de l'antiquité et qui n'avait cédé que sous la pression de connaissances nouvelles venues en foule et en ordre dispersé.

Il y a pourtant une différence fondamentale entre le genre d'unité qui se présente à nous actuellement, et le genre d'unité recherché par l'antiquité—et il faut bien le dire, par la Renaissance elle-même, et jusqu'à l'aube de la révolution scientifique du 17<sup>e</sup> siècle. Cette première unité était basée sur l'Homme, mesure de toutes choses, et individualité type. L'Homme devant se projeter sur l'Univers entier et se retrouver partout, dans le macroscopique du cosmos, dans le microscopique de l'atome. Ces atomes qui avaient les uns pour les autres des amitiés ou des haines. Maintenant, nous assignons à l'Homme une place plus limitée, parmi les organismes vivants, et c'est la Nature que nous projetons dans cet Homme, dans sa vie, dans sa pensée. L'antiquité tentait une biologie de la physique, de la chimie, de l'astronomie, tandis que nous tentons, vous tentez ici, une physique de la biologie—au moins d'une part aussi grande que possible de cette biologie. La jonction entre l'univers cosmique et atomique et le microcosme humain paraît devoir se faire en partant d'individualisations physico-chimiques moléculaires, caractérisées par des nombres précis, si complexes qu'ils puissent être, et en allant vers l'être vivant, virus, bactérie, cellule ou homme, à l'inverse de la recherche traditionnelle.



Cette marche décidée vers des généralisations précises et fécondes—au lieu des généralisations vagues et inhibitrices d'autrefois—cette ouverture sur des perspectives d'ensemble, ne signifie en aucune manière la disparition des spécialités et des spécialistes. Mais la spécialité est réservée à l'action, c'est-à-dire, à l'avance pas à pas dans la recherche. Nous sommes tous des spécialistes dès que nous agissons: spécialistes du volant sur la route, spécialistes de la pédagogie quand nous répondons aux nombreux "pourquoi" de nos enfants—ou petits enfants hélas pour moi,—ou même de la docimologie quand ces enfants nous présentent leur carnet scolaire. La docimologie est paraît-il la science de la notation des élèves, en particulier aux examens et concours. Nous sommes parfois de médiocres spécialistes, je le concède, dans ces activités, mais des spécialistes quand même. Or le physicien qui monte un appareil est électricien ou électronicien—et un bon spécialiste, s'il vous plaît, et plus tard un spécialiste des plaques nucléaires, des chambres à bulles, etc. La même chose vaut pour les chimistes et les biologistes, et je pense aussi pour les mathématiciens. Mais de plus en plus, dans la réflexion et la communication tout d'abord, dans l'expérimentation ensuite, nous trouvons des savants qui s'intéressent à la fois aux sciences dites exactes, mathématiques ou physiques, et aux sciences dites naturelles, c'est-à-dire aux aspects divers de la biologie. Mieux encore, des physiciens deviennent des biologistes, comme nous avons vu des mathématiciens devenir psychologues, ou des philosophes devenir ethnologues et apporter dans ces sciences de véritables révolutions.

En réalité, il ne s'agit pas de nouvelles rencontres, mais de véritables retrouvailles. N'oublions pas que Galvani était médecin et physicien, ce qui lui permit de mettre la biologie des cuisses de grenouille au service de la physique de jonction métallique et de découvrir le principe des piles électriques. Que Mayer, médecin, découvrit le principe de conservation de l'énergie, que Pasteur, chimiste, fonda la microbiologie et l'immunologie. Plus près de nous Schrödinger, Gamow, physiciens, s'intéressèrent à la génétique.

Mes chers collègues, tout ceci me fait penser à une remarque très pénétrante faite par un de mes amis, diplomate, qui se trouva placé professionnellement en contact avec des savants atomistes. "Je n'ai aperçu le véritable sens social de la science," m'a-t-il dit, "que le jour où j'ai compris que les scientifiques de par le monde étaient tous membres d'un même club." Un club sans réglementation écrite, sans formalisme à l'entrée ni cotisations annuelles, un club tacite en quelque sorte, mais cependant très fermé à ceux qui ne sont pas qualifiés pour en faire partie. Un club d'extension mondiale et dont l'influence, pour ne pas être souvent très apparente, n'en est pas moins considérable. Eh bien, vous formez ici un brillant échantillonnage des membres du club en question, venus ici à l'invitation de l'Institut de la Vie, pour confronter et échanger vos idées sur cette vie, justement, ou au moins sur certains de ses aspects qui paraissent les plus accessibles.

Au nom des membres du club mondial des scientifiques réunis ici, Monsieur le Ministre, je vous remercie encore une fois de nous avoir fait l'honneur de prendre place parmi nous et aussi d'avoir bien voulu m'écouter avec tant de patience.

### *Allocution de MAURICE SCHUMANN*

Si l'on a vu des naturalistes devenir des chimistes, on a vu aussi des littéraires devenir ministres de la Science! Aussi ai-je eu tout à l'heure le sentiment d'être visé, quand mon ami, le Pr. Auger, s'est adressé à certains d'entre nous en les appelant "Messieurs les élèves". Nous allons voir si je suis un assez bon élève pour avoir compris le raisonnement que le Pr. Auger a tenu tout à l'heure et que je me suis efforcé de saisir au vol. D'une part, la biologie exprime, ou commence à exprimer les phénomènes vitaux en langage moléculaire. Et d'ailleurs Pr. Auger nous a lui-même cité un brillant exemple, en évoquant les acides ribonucléiques, le rôle qu'ils jouent dans la production des cellules. D'autre part, la physique théorique progresse, et progresse même rapidement dans la représentation des molécules: elle interprète les propriétés des molécules en langage mathématique. Par conséquent, le lien entre la biologie et la physique théorique est le lien entre le phénomène vital et le langage mathématique. C'est alors que surgit la grande question: va-t-on mettre, allez-vous mettre ou tenter de mettre la vie en équations? Allez-vous confier ces équations aux machines à calculer, qui effectuent plusieurs millions d'opérations en une seconde? Allez-vous, allons-nous ramener les phénomènes physiques à des déplacements d'électrons?

Et aussitôt surgit, à peine modifiée, la question que Jean Rostand posait, avec angoisse, lorsqu'il se demandait si l'homme était capable de prendre en main les commandes chimiques de son destin. Nous pourrions dire: l'homme est-il capable de prendre en main les commandes physiques de son destin? Y a-t-il une désintégration de l'homme parallèle à la désintégration de la matière? Dès que je pose cette question trois réponses me rassurent. Ces trois réponses se réfèrent à trois thèmes auxquels il m'arrive maintenant de penser chaque jour.

Le premier de ces trois thèmes—puisque je viens de parler de machines électroniques—est ce que l'on appelle désormais, d'un mot international, le "software". Je veux dire (nous voulons dire) l'ensemble des connaissances qu'il faut posséder pour appliquer les dispositifs techniques au traitement de l'informatique. Quelque chose d'infiniment rassurant à constater est que le "software", c'est-à-dire la part irréductible de l'intelligence humaine et du cerveau humain, entre pour 60%, d'après les estimations les plus récentes, dans le coût total de ces machines, dont certains se demandaient si elles n'avaient pas pour objet de rendre, à la limite, le cerveau humain inutile.

Le deuxième élément qui me rassure, c'est ce que je tends à appeler, de plus en plus, "la prédominance de l'application sur l'explication". A mon tour, je m'explique. Et je m'explique en raisonnant, si vous le voulez bien, par analogie. . . . En fait, nous ne savons pas désintégrer, c'est-à-dire faire disparaître, en la transformant en énergie, n'importe quelle masse, ou n'importe quelle matière.

Nous savons obtenir de l'énergie avec une petite partie de la masse d'un élément naturel. En réalité, on ne fait pas disparaître de la matière, mais on modifie la composition des noyaux et en conséquence l'énergie de liaison qui soude entre elles les particules des noyaux. De même, on peut bien me dire qu'un individu qui pèse 100 kilos contient 63 kilos d'oxygène, 19 de carbone et 9 d'hydrogène. Mais on me dit pas comment les cellules peuvent constituer un cœur qui bat, une main qui écrit, une bouche qui parle, ou un cerveau qui pense. Ce qui revient à dire que le vrai mystère ne recule pas. Me dira-t-on qu'il en ira autrement si l'on se situe au niveau ou au sein même des molécules? Assistera-t-on alors à des expériences qui permettront d'assimiler aux phénomènes physicochimiques le mécanisme intime de la vie? Mon sentiment est que le vrai triomphe est ailleurs, et que le titre même d'Institut de la VIE, qui nous rassemble ce soir, l'exprime. Le vrai triomphe, vous le remportez (pardonnez-moi, mes chers Maîtres cet apparent pragmatisme) quand vous déchiffrez le code génétique, quand vous prévoyez les modifications de l'hérédité, la guérison de certaines maladies, peut-être même du cancer, quand vous donnez les formules des acides nucléiques. Je songe, par exemple, à ce laboratoire de Chimie moléculaire, où peut-être, à l'heure où nous parlons, on est en train de choisir les types de molécules, qui, une fois marquées et chargées de radioisotopes, permettront non seulement de dépister les cancers, mais encore, fixées sélectivement sur les tumeurs, d'en accélérer la guérison. Vous allez en somme plus loin sur la voie de l'action bienfaisante que sur celle de l'explication totale. Et la Mathématique est l'outil avec lequel vous transformez le monde des réalités vivantes, comme elle fut l'outil avec lequel la Science a transformé le monde des réalités inertes.

Enfin, ma troisième et dernière réponse, donc ma troisième et dernière consolation, est ce que M. Auger appelait tout à l'heure le "Club". Je veux dire cette universalité de la recherche dont vous êtes les témoins et dont la découverte est si réconfortante pour un homme public, qui, quand le bonheur lui échoit d'être ministre de la Science, se dit qu'il peut et qu'il doit aller dans les capitales les plus diverses, pour y tenir et y entendre le même langage, pour y asseoir la coopération technique et scientifique sur les mêmes bases. En ce sens, le temps revient où Mersenne correspondait avec Torricelli, Leibniz avec toute l'Europe, le temps même un peu plus proche où, en pleine guerre napoléonienne, le physicien anglais Davy venait tout près d'ici pour recevoir un prix de l'Institut de France. Mettre "non la vie en équation mais l'équation au service de la vie": voilà l'enseignement de vos travaux, voilà peut-être aussi votre devise! Nul ne l'a mieux illustrée que Teilhard de Chardin, quand, dans une belle phrase qui fut mise symboliquement en musique, transformée en cantate par André Jolivet, il disait: "Jusqu'au dernier moment des siècles, la matière sera jeune, exubérante, étincelante et nouvelle... pour qui voudra!"

*Allocution de S. L. SOBOLEV*

Après d'aussi brillants discours, le modeste mathématicien que je suis n'ose plus même évoquer d'aussi vastes questions. Participant à un si important Colloque, je parlerai cependant, pour dire toute ma reconnaissance à M. Marois, à M. le Ministre, à tous ceux qui ont fait, de notre séjour à Versailles, une détente si agréable.

Comme mathématicien, j'ajoute que certaines questions ne peuvent être résolues dès maintenant par la physique théorique ou expérimentale, ni par la biologie; elles nécessitent l'apport de nouvelles idées, qui ne peuvent venir que des mathématiques. L'histoire nous en donne de nombreux exemples. Aucune grande découverte, dans les sciences, techniques ou naturelles, et autres, qui n'ait été précédée d'un demi-siècle de recherche mathématique! Tout le monde se moquait, disant que cette recherche était inutile et sotte. C'était l'exemple d'une géométrie non euclidienne, qui "ne pouvait être sérieuse". Mais quand, après soixante ou soixante-dix ans, fut élaborée la théorie de la relativité, tout le monde comprit que c'était vrai, et très intéressant.

Je ne suis qu'un modeste mathématicien, mais je ne suis pas très modeste quand je parle mathématiques!

*Address by R. S. MULLIKEN*

After the preceding speakers, there is very little I could say, even if I were good at after dinner speaking. However I would like to express that this is the most interesting conference I have ever attended, with such a remarkable group of people of which some are old friends and some of them new friends. I congratulate the Committee and I thank Professor Marois and his collaborators and the Committee and I think I speak also on behalf of others who speak english in this respect.

*Allocution d'ouverture de la Conférence par PIERRE-P. GRASSÉ*

Mesdames, Messieurs,

C'est un grand honneur que de vous souhaiter la bienvenue. Pour venir à nous vous avez affronté les fatigues d'un long voyage et avez consenti à nous consacrer quelques jours d'un temps dont nous connaissons tout le prix. Au plaisir de vous accueillir s'ajoute un sentiment de sincère gratitude.

Nous mesurons aussi l'honneur que vous faites en acceptant de participer à cette conférence qui est vraiment vôtre. Plusieurs d'entre vous portent les noms les plus glorieux de la science contemporaine et rendent, par leur collaboration, un hommage aux chercheurs français qui en sont à la fois heureux et fiers.

Le comité organisateur de cette conférence tient à ajouter à ses remerciements l'assurance que tout sera mis en oeuvre pour que votre séjour à Versailles soit agréable et fructueux.

La science d'aujourd'hui perd de plus en plus le caractère strictement individuel qu'elle a présenté pendant des siècles. Ce n'est point tant au travail en équipe que nous faisons allusion qu'à l'impossibilité pour l'homme d'absorber, de s'assimiler une quantité illimitée de connaissances. Manque de temps, insuffisance de la mémoire, pour tout dire impossibilité physiologique de faire enregistrer par le cerveau la masse de faits, lois et expériences qui constituent une science. Le temps où un Buffon possédait la quasi-totalité du savoir scientifique de son temps, des mathématiques à l'histoire naturelle, est bien révolu. L'homme de science, si érudit soit-il, devient, souvent malgré lui, un spécialiste.

Pour que l'indispensable synthèse ne soit pas étouffée sous le poids des connaissances dont l'accroissement va s'accéléralant du fait de l'augmentation continue du nombre des chercheurs, il faut, de toute nécessité, recourir aux moyens propres à la maintenir possible. La multiplication des colloques, la rédaction de livres collectifs tendent à pallier les inconvénients de l'inéluctable spécialisation.

On ne peut douter que la rencontre d'aujourd'hui ne tende vers ce but, mais selon moi, elle a une fin plus importante et plus originale.

La biologie, science encore au début de son développement, considère les objets les plus complexes existant dans notre système solaire. Ses moyens ne sont pas proportionnés à la grandeur et à la difficulté de sa tâche; elle travaille presque toujours à tâtons car elle ne connaît que rarement la totalité des facteurs et des causes qui interviennent dans le déterminisme et le déroulement des phénomènes qu'elle étudie.

Les progrès des sciences de la vie furent très lents et c'est seulement depuis quelques années qu'ils se sont précipités. N'oublions pas que pendant des siècles, les phénomènes vitaux furent tenus comme irréductibles aux phénomènes physiques

ou chimiques: la vie étant la propriété de corps, ou organismes essentiellement différente des propriétés que possèdent les corps inertes. Aujourd'hui, nous savons que les phénomènes vitaux s'inscrivent sans aucun doute parmi les manifestations physico-chimiques mais que les réactifs, les appareils dont disposent les êtres vivants diffèrent de ceux qu'utilise ordinairement le physicien ou le chimiste dans son laboratoire. Cette originalité qui, sans doute, a sa valeur, n'autorise nullement à isoler les phénomènes vitaux dans une catégorie particulière.

Ainsi, d'emblée, l'union du physicien, du chimiste et du biologiste s'impose pour toute étude exhaustive et synthétique des phénomènes vitaux. Tandis que le biochimiste découvrait la vraie nature des constituants des êtres vivants et poussait son investigation jusqu'au niveau de la molécule, les biologistes, grâce au microscope électronique observaient, enfin, ces mêmes constituants sous leur forme réelle et, dans bien des cas, en voyaient les macromolécules constitutives.

Ainsi, peu à peu, l'intérêt s'est porté sur les phénomènes biologiques considérés à l'échelle moléculaire d'où la naissance d'une nouvelle discipline: *la biologie moléculaire*. La connaissance de la molécule de diverses protéines, d'hormones et des acides nucléiques a donné un grand élan à cette jeune science, qui, tout en suivant le déroulement des phénomènes au sein de la cellule, en définit les phases successives en termes physiques et chimiques.

Mais, dès maintenant, bien des chercheurs estiment que les constituants des êtres vivants doivent être étudiés au niveau des corpuscules. De ce fait, ce n'est plus à la physique classique que l'on doit recourir mais à la physique quantique. Nombreux sont les physiciens qui considèrent celle-ci comme étant la plus apte à expliquer les mécanismes biologiques.

Les phénomènes tels que les attractions qui s'exercent entre les chromosomes et entre les gènes homologues, l'influence des centrosomes, la production des mutations ressortissent, semble-t-il, à la fois de la biologie moléculaire et de la physique quantique. On pressent qu'il en va de même pour les phénomènes de la vision et de la mémoire. Les premières applications de cette physique à l'étude des acides nucléiques sont fort encourageantes et on a, dès maintenant, l'impression qu'elles ouvrent de nouvelles voies à la biologie. L'ère de l'application de la physique théorique à la biologie est donc ouverte.

Les nouvelles techniques, les nouveaux appareils ont permis à la biologie de progresser à pas de géant, mais ils ne doivent plus être les seuls à l'aider. Quelques hommes se sont demandés si une forme particulière de biologie qui ferait pendant à la physique théorique ne pourrait pas être édifiée et projeter une vive lumière sur des parties encore obscures du domaine de la vie. Bien que les premiers essais n'aient pas été entièrement concluants, ils ont été suffisamment positifs pour que de nouvelles tentatives soient entreprises avec des chances de succès.

La physique théorique peut apporter un concours extrêmement précieux à la jeune biologie qu'elle soit théorique ou non; son champ d'action déborde largement les propriétés de la matière inerte et tend à atteindre les manifestations

de la vie. Pour ces raisons, notre rencontre prend à mes yeux une valeur particulière, en quelque sorte symbolique. Elle annonce que physique théorique et biologie contractent une union étroite et définitive. Elle marquera une date dans l'histoire des sciences.

Je vous remercie, Messieurs, de l'attention que vous m'avez prêtée. Je déclare la conférence ouverte et je transmets la présidence au Professeur Rosenfeld.

*Allocution d'ouverture de la première séance par L. ROSENFELD*

We must be extremely grateful to the Institut de la Vie for bringing us here together. This is not a conference of the usual kind. It is actually a kind of experiment in establishing contact between two branches of science which so far have developed rather independently of each other, with different methods, but which are now converging towards a common ground. It is with great expectation that I personally am looking forward to the way in which this dialogue is going to take place. It is up to us to make a success of it, as I very much hope we shall. It may be the beginning of a co-operation of which one may hope that it will accelerate the spectacular progress that has been made in recent years.

As a physicist I may add that so far the biologists have managed quite well without the help of the physicists. I have the greatest admiration for the way in which they have disentangled the very deep-lying problems of molecular biology, and especially the logical problems connected with the reading of the genetic code. I think this is a tremendous achievement. We physicists, if I may also speak for my colleagues, are approaching this conference in a very humble spirit. We shall see how things will develop, according to the program in which the physicists have been given the word right at the start.

*Journée du 26 juin 1967*

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## CONCEPTS THEORIQUES

*1ère séance*

PRÉSIDENT L. ROSENFELD

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H. FRÖHLICH

Quantum Mechanical Concepts in Biology

I. PRIGOGINE

Structure, Dissipation and Life

Discussions



## QUANTUM MECHANICAL CONCEPTS IN BIOLOGY

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### 1. Introduction

In many macroscopic properties of materials quantum mechanics shows its influence only in an indirect way namely through the properties of the atoms of which the substance consists. A notable exception is formed by the specific heat at very low temperatures which for the first time demonstrated quantization on a macroscopic scale. In recent years discussion of certain other low temperature phenomena has shown them to exhibit effects which might best be described in terms of macroscopic quantization of a more subtle nature giving rise to an order of a new kind based on the concept of phase correlations. I believe that this concept may have a much wider range of application in particular in systems which are relatively stable but not near thermal equilibrium, and which show an organised collective behaviour which cannot be described in terms of an obvious (static) spacial order. In the following I shall first describe these concepts in a general way, and then present a speculative model which might be applied to biological systems.

### 2. Long range phase correlations

All materials are composed of atoms. Complete solution of the equations describing their dynamic behaviour would, however, yield such an immensity of irrelevant information that selecting from it the features of interest would be prohibitive. For the number of states of a system increases exponentially with the number of particles it contains; adding two particles would at normal temperatures increase the number of its states about 100-fold!

Clearly establishment of a useful connection between micro and macro physics requires introduction of relevant macroscopic concepts, and their expression in terms of microscopic (atomic) features. In terms of the latter, macro concepts are always "collective" properties. This programme is well advanced when dealing with behaviour near thermal equilibrium. Relevant concepts are the thermodynamic ones (free energy, entropy, etc.), hydrodynamical fields, properties of spacial order (crystal structure, etc.) etc. The study of the peculiar phenomena of superconductivity and superfluidity have revealed, however, existence of a macroscopic spacial order which is not of such an obvious nature and which is best described in terms of certain quantum mechanical concepts on a macroscopic scale.

Quantum mechanics treats the dynamic behaviour of any system in terms of a state vector (or wave function)  $\Psi$ . For a single particle this is essentially a de Broglie wave, but it is much more complicated for a system of many particles. It is essential that this  $\Psi$  is a complex quantity, and that its absolute square describes a certain probability and is the quantity normally used in comparison with experiments. Multiplication of this  $\Psi$  by a phase factor say  $e^{i\alpha}$  does thus not alter the relevant probability. A second essential feature of quantum mechanics is, however, that the state vectors of two (or more) states can be superimposed linearly to form a combined state; the absolute square (probability) of this combined state thus depends on the difference of the phases of its components. This expresses a typical wave interference, characteristic for quantum mechanics.

In very large systems, owing to thermal disorder such phase differences frequently average out and lead to no observable result. In fact it can be shown that establishment of a "pure" state, i.e., one exhibiting a definite phase, in a macroscopic body would require times which are long even compared with cosmological ones. Nevertheless significant exceptions to the absence of a definite phase in a macro-system exist. They are, however, always connected with a very strong excitation of one or a few modes of motion; and their phases then show correlations over macroscopic regions. It is not the state function  $\Psi$ , therefore, that we are concerned with but rather a much simpler quantity, a macroscopic wave function, say  $\Phi(x)$  which persists after the appropriate thermal averaging has been performed. While  $\Psi$  depends in a complicated way on the coordinates of all the particles composing the substance, the macrowave function  $\Phi(x)$  simply depends on space, time and a few parameters.

A formal procedure exists of how one would derive existence of macro wave functions from the most general microscopic description of the system (use of Von Neumann's density matrix to form reduced density matrices [1]). This can be applied to specific systems but a general treatment has so far not been found. Clearly establishment of one or a few strongly excited modes of motion requires their stabilisation. In the mentioned low temperature phenomena this is achieved for energetic reasons. At normal temperatures, however, such excited states can be only metastable. Thus e.g. if a macroscopic sound wave is imposed on a material then clearly macroscopic classical phase relations exist for the density at various space points. This means that a phase correlated motion is superimposed on the irregular thermal motion of the atoms, and a macroscopic wave function then exists -- formally derived by a procedure similar to the one used for superconductors.

A more subtle example is provided by laser states [4]. A strongly excited (transverse) electromagnetic wave imposes here the relevant long range phase correlations on the thermal motion. A material thus excited will ultimately emit as light the energy stored in the relevant modes. Another possibility exists, however, namely strong excitation of longitudinal electric waves. Light waves are transverse

electromagnetic waves. Longitudinal waves cannot exist in vacuum and hence cannot be emitted. They exist, however, in materials at selected frequencies. These frequencies are in some way correlated to the resonance frequencies for transverse waves, but they are higher by a definite amount. If the corresponding transverse frequency is very low (or zero) then the correlation between longitudinal and transverse modes becomes rather artificial. Such longitudinal modes once strongly excited have a relatively high stability because they cannot lose energy by emitting radiation. If their frequency is relatively low, however, then energy may be lost by ordinary friction. In this case, however, another stabilising mechanism arises, in certain circumstances, in terms of internal deformations.

### 3. Application to biological systems

Biological systems exhibit relative stability in a way in which some modes of behaviour remain very far from thermal equilibrium although from an atomic point of view the majority of the degrees of freedom behave like being close to thermal equilibrium. It is tempting, therefore, to postulate the existence of long range quantum mechanical phase correlations in biological systems. (Per-Olov Löwdin has informed me that he has made such a proposal three years ago). It must be realised, however, as pointed out in the previous section that the phase of the quantum mechanical state vector is averaged out by the thermal motion of the many atoms. Nevertheless we have seen that phase correlations may persist even after the averaging over thermal motion, provided a few modes of motion are very strongly excited. The strong polar character of biological objects suggests longitudinal electric oscillations as stabilising modes.

One can imagine two types of sources for these oscillations. One would be connected with certain molecular processes involving ions. The second would be characteristic of the cell as a whole. The two types might be in resonance.

The frequencies involved in molecular processes cover a very wide range. An estimate of the frequencies of the second type of oscillations might be given because some of these at least should involve the cell membrane which has a strong dipolar layer of thickness of order  $10^{-6}$  cm. A localised vibration would correspond to a frequency  $\nu$  of order  $10^{11}$  sec $^{-1}$  (assuming elastic constants corresponding to a sound velocity of order  $10^5$  cm/sec). If some molecules in the cell would contain effectively free electrons then resonance would require a number density  $n$  of order  $10^{14}e$  per c.c. ( $e$ =effective dielectric constant;  $\nu^2 = e^2n/\pi m\epsilon$ ;  $m$ =electron mass). Some molecular processes would, however, lead to much higher frequencies.

Establishment of strong excitation of some modes would require that certain biological processes feed energy into these modes, and that frictional losses are relatively small so that a stabilisation can take place. This could be achieved through elastic deformations which change the dielectric properties in such a way

that the strongly excited longitudinal electric vibrations would become "frozen in", i.e., a metastable state of equilibrium would be achieved. For a system of cells this is feasible on condition that (i) the vibration is sufficiently strongly excited, and (ii) the cells are not too densely packed.

What conclusions would one draw from establishment of these vibrations?

(i) On a molecular basis they would impose the "correct" frequency though what this actually implies would require detailed investigation.

(ii) On an individual cell, the deformation required for stabilisation would impose a stress at the surface which would increase with increasing size. It could thus act as a stimulus for cell division.

(iii) When the cells are densely packed then the stabilising mechanism through deformation no longer works, and the electric field must then collapse. With it would then vanish the stimulus for cell division.

(iv) Possible absorption in the medium will define a range for the correlations and might hence influence macroscopic size effects.

Clearly it would be desirable to attempt measuring the conjectured longitudinal electric vibrations. Their effectiveness is based on the long range coherence which implies that the energy content of these vibrations is concentrated into very narrow frequency ranges. This makes measurement, of course, difficult because although the energy per unit frequency would be high, the total energy contained in such a mode would be very low, compared with say the total thermal energy.

In conclusion I wish to remark that the above suggestions are meant to be highly speculative. They should demonstrate, however, that application of quantum mechanical concepts can lead to new points of view which might be used as guiding points in the search for undiscovered regularities.

#### *Appendix I: Shape dependence of the free energy in the presence of longitudinal electric oscillations*

Consider a model in which a number of units (cells) are distributed in a continuous medium. If these units have a longitudinal resonance frequency then the total polarisation can be considered as superposition of contributions from the background,  $P_0$ , and from the resonance,  $P$ , such that the free energy becomes also a sum of two such contributions. A particularly simple example of such a superposition is treated in the theory of polarons [2]. In the region of linear response the contribution of the resonance oscillations to the free energy is

$$U_P = \sum cf(a) a^3 \overline{P^2}. \quad (1)$$

Here  $a^3$  is of order of the volume of a given unit,  $f(a)$  describes their size distribution such that

$$n = \sum f(a)$$

is their total number, and  $c$  is a number;  $\overline{P^2}$  is the mean of the oscillating  $P^2$ .

In the case of plasma oscillations in cells one would expect a non-linear response at fairly low polarisation. The direction of the influence of deformation can, however, be demonstrated even for still weaker polarisation for which (1) holds. The reason is that the constant  $c$  depends on the shape of a unit provided the units are sufficiently separated. Thus if we assume the units in the absence of a polarisation to be spherical, the deformation into ellipsoidal shape will change the energy expression into

$$U_P = c \sum f(a) a^3 \overline{P^2} (1 - \alpha \eta_a), \quad (2)$$

where  $\eta_a$  is the eccentricity, and  $\alpha$  is of order one. Note that  $\eta_a$  may be positive or negative. The relevant free energy will thus be smaller than in the undeformed case if  $\eta_a > 0$ . This deformation is opposed by the elastic surface energy which in the absence of polarisation must have been a minimum with respect to deformation, and hence must be proportional to  $a^2 \eta_a^2$ . The total free energy thus becomes

$$U = \sum \{c a^3 \overline{P^2} (1 - \alpha \eta_a) + \frac{1}{2} S a^2 \eta_a^2\} f(a), \quad (3)$$

where  $S$  is related to the surface elastic constants.

We should now minimise  $U$  with regard to the displacements  $\eta_a$ . This results in

$$\eta_a = \alpha c \overline{P^2} a / S, \quad (4)$$

so that

$$\frac{1}{n} U = c \overline{P^2} a^3 - \frac{1}{2} \frac{\alpha^2}{S} (c \overline{P^2})^2 \overline{a^4}, \quad (5)$$

where

$$\overline{a^n} = \sum a^n f(a). \quad (6)$$

Thus, owing to the deformation, expression (1) for the undeformed energy is reduced by an amount proportional to  $(\overline{P^2})^2$ . We also note that the stress parameter  $\eta_a$  of an individual unit increases with its size  $\propto a$ .

One could now, of course, find the polarisation  $P_m$  at which  $U$  reaches a maximum and beyond which  $U$  thus decreases with increasing  $P^2$ . This would yield

$$c \overline{P_m^2} = \frac{S}{\alpha^2} \frac{\overline{a^3}}{\overline{a^4}} \quad (7)$$

and hence

$$\alpha \eta_{m,a} = \frac{\overline{a a^3}}{\overline{a^4}}, \quad (8)$$

so that the first term in (3) would vanish at this point.

Such considerations, however, would be unrealistic. For not only would the linear and the quadratic in  $\eta_a$  approximation used in (3) have become invalid, but also the assumption of linear response may no longer hold. Under such circumstances the neglected terms should influence the position of the maximum, and would also lead to a subsequent minimum unless the units were destroyed. At this minimum the assembly would then be in a metastable state with frozen-in polarisation waves.

The above considerations also break down if the units are closely packed. For if as a limiting case we would assume the units to be cubic then close packing would provide a homogeneous material and the question of shape dependence could not arise. In actual calculations the influence of the packing density would arise from considerations referring to the *local* field.

Finally it should be mentioned that on the basis of the polaron model mentioned above the constant  $c$  would be proportional to  $\varepsilon\varepsilon_0/(\varepsilon - \varepsilon_0)$  if  $\varepsilon_0$  is the static dielectric constant of the background, and  $\varepsilon$  that of the whole substance. The smaller  $(\varepsilon - \varepsilon_0)$ , therefore, the more sensitive would the energy be to changes in parameters.

## Appendix II

According to C. N. Yang [1] and to Penrose and Onsager [2] superfluids show a long range phase correlation which can be defined in terms of a reduced density matrix

$$\Omega_{\text{red}}(x', x'') = \text{Sp } \psi^*(x'') \psi(x') \Omega, \quad (1)$$

where  $\Omega$  is von Neumann's density matrix,  $\psi^*(x)$ ,  $\psi(x)$  the wave operators of the particle field constituting the superfluid;  $x'$ ,  $x''$  are space points and Sp represents the trace. For superfluids then

$$\Omega_{\text{red}}(x', x'') = \Phi^*(x'') \Phi(x') + \chi(x', x''). \quad (2)$$

$\Phi(x)$  represents a macro wavefunction, and  $\Phi^*(x'') \Phi(x')$  is large compared with  $\chi(x'', x')$  if  $|x'' - x'|$  is large compared with atomic dimensions.

A corresponding relation holds for superconductors but requires a second reduced density matrix (2nd order in  $\psi$  and  $\psi^*$ ).

We shall show that quite a similar relation exists for a material in which a macroscopic sound wave is excited. First note that for a material with sound velocity  $s$  consisting of  $N$  atoms of mass  $M$  the operator

$$b = \left( \frac{Ms}{2\hbar k N} \right)^{\frac{1}{2}} \sum_j \left\{ e^{-ikx_j} \left( 1 + \frac{uv_j}{s} \right) + \left( 1 + \frac{uv_j}{s} \right) e^{-ikx_j} \right\} \quad (3)$$

represents a destruction operator of phonons (quantised sound waves) of wave number  $k$ . Here  $x_j$  is the coordinate of atom  $j$ , and

$$u = \frac{k}{k}, \quad v_j = -\frac{i\hbar}{M} \frac{\partial}{\partial x}. \quad (4)$$

We note that the usual commutator

$$(b, b^*) = 1 \quad (5)$$

holds.

Also if  $\Omega_0$  is the density matrix when no sound wave is excited macroscopically then

$$\text{Sp } b^* b \Omega_0 = n_k \quad (6)$$

represents the mean number of thermal phonons of wave number  $k$ , i.e. a number of order 1, corresponding to an energy  $\hbar k s n_k$ .

Also we expect

$$\langle b \rangle = \text{Sp } b \Omega_0 = 0, \quad \langle b^* \rangle = \text{Sp } b^* \Omega_0 = 0, \quad (7)$$

or more general

$$\text{Sp } b^{*n} b^m \Omega_0 = \delta_{n,m} n! \quad (8)$$

to hold in good approximation, as for harmonic oscillators.

If  $V$  is the total volume then

$$b(x) = b \frac{e^{ikx}}{\sqrt{V}}, \quad b^*(x) = b^* \frac{e^{-ikx}}{\sqrt{V}} \quad (9)$$

define wave operators at  $x$ . Their expectation values vanish in a state  $\Omega_0$  in view of (7).

If a macroscopic sound wave is excited then the amplitudes  $\langle b \rangle$ ,  $\langle b^* \rangle$  should not vanish but be periodic in time, and the energy should be proportional to the volume  $V$ . Such a state can be described by a density matrix

$$\Omega = T \Omega_0 T^*, \quad (10)$$

where the operators  $T$  and  $T^*$  are given by

$$T = C e^{-\frac{1}{2}\beta\beta^*} e^{\beta b^*}, \quad T^* = C^* e^{-\frac{1}{2}\beta\beta^*} e^{\beta^* b}. \quad (11)$$

Here  $\beta$  and  $\beta^*$  are time dependent  $c$ -numbers,

$$\beta = \beta_0 e^{ikst}, \quad \beta^* = \beta_0^* e^{-ikst} \quad (12)$$

and the numbers  $C$  and  $C^*$  are to be chosen such that

$$\text{Sp } \Omega = 1 \quad \text{when } \text{Sp } \Omega_0 = 1. \quad (13)$$

Particularly simple is the case in which  $n_k=0$ , for then  $C=1$ ,  $C^*=1$ . We note the relations

$$(b, T) = \beta T, \quad (T^*, b^*) = \beta^* T^* \quad (14)$$

and using (8) and (5)

$$\text{Sp } T^* T b \Omega_0 = \text{Sp } T b \Omega_0 T^* = 0. \quad (15)$$

We thus find from (13)-(15)

$$\begin{aligned} \langle b \rangle &= \text{Sp } b \Omega = \text{Sp } b T \Omega_0 T^* \\ &= \text{Sp } (b, T) \Omega_0 T^* + \text{Sp } T b \Omega_0 T^* = \beta. \end{aligned} \quad (16)$$

Hence also

$$\langle b^* \rangle = \beta^* \quad (17)$$

and

$$\begin{aligned} \text{Sp } b^* b \Omega &= \text{Sp } b \Omega b^* = \text{Sp } ((b, T) + T b) \Omega_0 ((T^*, b^*) + b^* T^*) = \\ &= \text{Sp } (\beta + T b) \Omega_0 (\beta^* + b^* T^*) = \beta^* \beta + n_k. \end{aligned} \quad (18)$$

An energy proportional to the volume thus requires  $\beta$  proportional to  $\sqrt{V}$  i.e.,

$$\beta = B \sqrt{V}, \quad (19)$$

where  $B$  is volume independent. From (9) we then have

$$B(x) = \text{Sp } b(x) \Omega = B e^{ikx}. \quad (20)$$

A reduced density matrix  $\Omega_s(x', x'')$  can thus be defined as

$$\Omega_s(x', x'') = \text{Sp } b^*(x'') b(x') \Omega \quad (21)$$

in terms of  $\Omega$  and individual particle operators  $x_j$ ,  $\partial/\partial x_j$ ;  $\Omega_s$  can also be written in terms of the particle field operators  $\psi$ ,  $\psi^*$ ; It then represents a second reduced density matrix. We note from (18)-(20) that

$$\Omega_s(x', x'') = B^*(x'') B(x') + n_k \frac{e^{ik(x''-x')}}{V} \quad (22)$$

has the form required by (2).

## SUMMARY

Quantum mechanics has led to an understanding of the properties of atoms and of their interactions. It is often argued that the properties of all materials could, therefore, be derived automatically if only one could master the mathematical techniques required to handle systems composed of a very great number of individual atoms. This conclusion is at fault for complete solution of such complex problems would provide us with an enormous number of informational



facts, nearly all of them irrelevant for most purposes. The task of selecting from them the features of interest to a physicist and to a biologist would be of the same order of complication, roughly speaking, as finding complete solutions in the first place. It has been realized, therefore,—by some physicists at least—that the first task in attempting treatment of a many body problem must lie in the formulation of appropriate questions.

Amongst the biological features particularly striking to physicists is the relative stability of systems in which some modes of behaviour remain very far from thermal equilibrium; another is the apparently strongly correlated behaviour of large systems consisting of a number of individual units—as demonstrated, for instance, in the growth of an organ (consisting of many units, the cells) which is discontinued after a certain roughly defined size and shape has been reached.

Physicists have, of course, for many years dealt with the collectively organised behaviour of assemblies of many units; but until quite recently such treatments were always connected with some long range spacial order of a rather obvious kind. More recently, however, new features have arisen which refer to fluid systems possessing no *obvious* long range spacial order. These features have been formulated in context with superfluidity (a property of liquid helium) and with superconductivity (a property of the electron “fluid” in metals). In the empirical formulation of C. N. Yang [1] they can be expressed as a long-range phase correlation in terms of the so called density matrix, the quantum mechanical quantity from which all features of a large system can be derived in principle. Existence of these phase correlations is, roughly speaking, equivalent with the existence of macro wave functions. They imply establishment of rather subtle, long-range, correlations in a phase which has no immediate physical significance, but from which superfluidity and superconductivity follow. These latter properties exist at very low temperatures only. I believe, however, that existence of these long range phase correlations (coherence) have a very much wider range of application, in particular in systems in which some modes of behaviour are very strongly excited and stabilized far from equilibrium. An example are laser states [4].

I shall try to apply to biological systems the general ideas expressed above namely phase correlations on a macroscopic scale connected with some strongly excited (far off thermal equilibrium) modes of motion. Naturally—as is the habit in theoretical physics—a very much simplified model must be used to represent the common features of biological systems. A common property of cells which attracts the physicists attention is the electric double layer at the cell membrane which supports electric fields of the order  $10^5$  volts/cm. Oscillations of this membrane should, one can estimate, have frequencies of order  $10^{11}$  sec<sup>-1</sup>, or similar, and some of these oscillations must then have attached to them dipolar electrical oscillations; the frequencies correspond to electric waves in the mm or far infrared region. It might occur that some of the large molecules within the cell can resonate with these membrane oscillations and thus lead to electric dipole oscillations of the cell as a whole. The frequency or frequencies of these oscillations might be a characteristic property of a specific type of cell. An assembly of such cells suspended in a certain medium will no doubt exhibit the possibility of electrical oscillations. A long range phase correlation between cells would exist if one or a few of these modes were very strongly excited, far beyond the strength of thermal excitations, and if these excitations were relatively stable.

To investigate this possibility consider as a model a system of deformable spheres suspended in a medium of static dielectric constant  $\epsilon_0$ . The spheres are considered capable of electric dipolar oscillations as described above, and they will hence increase the dielectric constant of the system to a value  $\epsilon > \epsilon_0$ . The system as a whole will exhibit a number of modes of oscillations, amongst them certain longitudinal modes based on the electric dipolar oscillations of the respective units. Now it can be shown that in view of the deformability of the single units, the possibility exists that a single mode of longitudinal electric oscillation gets stabilized provided: (i) it is sufficiently strongly excited, and (ii) the units are *not* too densely packed. This means that with

regard to the particular mode of motion the system is very far from thermal equilibrium, i.e. that this mode contains relatively much energy. Stabilisation implies that this energy can only be lost by first supplying still more energy to this mode—much like a billiard ball can only move from the billiard table to the (lower energy) floor by first being lifted over the wall of the table to a higher energy. The stabilization is achieved by a certain deformation of the individual spherical unit under the influence of the high frequency electric polarisation  $P$  of the excited mode. This deformation is proportional to the mean square  $\overline{P^2}$  of the polarisation as it is too inert to follow the high frequency oscillations.

The above model consideration thus shows that a suspension of our units (cells) in an appropriate medium is capable of certain characteristic longitudinal electric vibrations and that strong excitation of one (or a few) of these modes may be relatively stable provided the density of our units is not too high.

Suppose we assume that existence of one or a few strongly excited relatively stable longitudinal electric modes in growing organs is established. What conclusions would we draw? Firstly "relatively" stable should mean that some supply of energy is still required to maintain and in particular to establish the vibration. I am told that a cell may be compared with a factory automatised for certain tasks expressed in terms of molecular processes.

(i) Some of these processes might be connected with the pumping of energy into the particular normal vibration of the organ as a whole. In return, once excited, the vibration of the organ would enforce vibration of the individual cell of the "correct" frequency.

(ii) Establishment of the strongly excited vibration would lead to a stress on the membrane surface and to the above mentioned deformation. The stress would increase with increasing size of the cell. It could thus act as a stimulus for cell division provided a particular cell is large enough.

(iii) With continuing growth the cells get packed more densely; the quasi stability of the strongly excited mode then gets gradually lost and finally a degree of density will be reached when the vibration can no longer be maintained. If the excited mode provides the stimulus for cell division (as supposed in (ii)) then at sufficiently dense packing this stimulus disappears and growth will stop.

(iv) Absorption in the medium will define a range for the phase correlations and might hence influence macroscopic size effects.

The above considerations are meant to be highly speculative. They should demonstrate, however, that application of quantum mechanical concepts to complex systems can lead to new points of view provided quantum mechanics is not used as the servant who tries to derive—with doubtful success—the value of some known parameters but is used as a guide capable of finding regularities hidden in a labyrinth.

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*Note added in proof:* I have now been able to show that non-linear interaction will lead to the channeling of supplied energy into coherent modes (*Intern. J. Quantum Chem.*, in press). For possible application in photosynthesis cf. *Nature* **219** (1968) 743.

## STRUCTURE, DISSIPATION AND LIFE

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### 1. Introduction

It is only too clear that there still exists a huge gap between biology and theoretical physics. This is not too astonishing: according to the opinion of some of the leading biologists [e.g. 1, 2], order both in its space and its functional aspect is the basic property of life. This is clearly a "many-body" problem as the formation and the maintenance of order involves the cooperation of a large number of molecules. However statistical physics which deals with such cooperative phenomena is still in its infancy. We only begin to understand even the simplest phase changes and the simplest hydrodynamic instabilities.

It is true that great advances have been made specially for phenomena near zero temperature (as superfluidity and superconductivity). However here we deal with essentially non dissipative "reversible" processes while in living systems metabolism and dissipation of energy is likely to play an essential role. For this reason my lecture will be based essentially on the use of phenomenological or thermodynamic methods. I would like to discuss in terms of such methods the source of biological order. I would also like to show that non-linear thermodynamics of irreversible processes as developed recently may narrow the gap between biology and physics.

As has been often noticed in macroscopic physics we may distinguish between two types of structure:

- a) equilibrium structures
- b) dissipative structures.

Equilibrium structures may be maintained *without any exchange of energy or matter*. A crystal is the prototype of an equilibrium structure.

Classical thermodynamics has solved the problem of the competition between randomness and structure (or "organization") for equilibrium situations: when we lower the temperature, the contribution of the energy to the Helmholtz free-energy

$$F = E - TS \tag{1.1}$$

becomes dominant. More and more complex structures corresponding to smaller

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entropy may then appear. To a phase transition such as crystallisation corresponds the loss of entropy

$$\Delta S = - \frac{\mathcal{L}_f}{T_m}, \quad (1.2)$$

where  $\mathcal{L}_f$  is the heat of melting and  $T_m$  the melting temperature.

On the contrary, "dissipative structures" are maintained only through exchange of energy (and in some cases also of matter) with the outside world.

A very simple example is a thermodiffusion cell in which a gradient of concentration is maintained by a flow of energy. Here we have already a dissipative process (exchange of heat) which leads to an increase of organization [3]. However, in this example, this increase occurs gradually with the increase of the gradient of temperature.

But discontinuous changes in structure due to dissipative processes are also possible. A simple example is the so-called "Bénard problem" in classical hydrodynamics [4]. We heat a horizontal fluid layer from below. We create in this way a so-called "adverse gradient" of temperature. For small values of this gradient the fluid remains at rest. But for a critical value of this gradient, there is an abrupt onset of thermal convection.

The role which the temperature played in the liquid  $\rightarrow$  solid transition is now played by the increase of the "constraint" which is here the adverse temperature gradient. The increase of this constraint leads from a situation in which the whole of the energy is in the thermal motion to a much more organized state in which part of it is in the form of macroscopic motion which is of course, a highly cooperative phenomenon from the molecular point of view.

The state of the fluid in the region of thermal convection may therefore be considered as an example of "dissipative structure". Its entropy is lower than that of a system in which the whole of the energy would be in the thermal motion. The corresponding loss of entropy is of the order

$$\Delta S = - \frac{E_{\text{kin}}}{\bar{T}}, \quad (1.3)$$

where  $\bar{T}$  is the average temperature characterizing the systems. The dissipative structure is achieved and maintained through the effect of the energy flow associated with the adverse gradient.

Are dissipative structures possible outside the range of hydrodynamics? What determines their occurrence? Before we try to give a more general answer to such problems let us consider a "chemical" example. We consider a sequence of reactions such as



The concentrations of the initial product  $A$  and of the final product  $B$  are fixed;  $X$  and  $M$  are intermediate components. We expect that for given values of  $A$ ,  $B$  the concentrations of  $X$ ,  $M$  will take well defined values in the steady state. For example, if we assume the simple kinetics laws (we put equal to one all equilibrium and rate constants)

$$V_1 = A - X, \quad V_2 = X - B, \quad V_3 = X - M, \quad (1.5)$$

we obtain easily at the steady state

$$M = X = \frac{1}{2}(A + B). \quad (1.6)$$

As a special case, (1.6) includes the case in which the fixed ratio  $A/B$  corresponds to thermodynamic equilibrium. Then  $B/A = 1$  and (1.6) reduces to

$$M = X = A = B. \quad (1.7)$$

The equilibrium result (1.7) could of course have been directly derived using the law of mass action. We may say that in this simple case the "thermodynamic solution" (1.7) may be "extended" to the whole possible range of the constraint  $A/B$  to obtain (1.6). However in general if we use a more complicated non-linear scheme of reactions there may be different time-independent solutions of the kinetic equations.

$$\frac{dX}{dt} = 0, \quad \frac{dM}{dt} = 0, \quad (1.8)$$

all satisfying obvious physical conditions such as the concentrations to be real, positive quantities. Let us call these solutions  $X_1, \dots, X_2; M_1, \dots, M_2$ . One of them, say  $X_1$ , contains as a special case the equilibrium solution corresponding to a minimum of free-energy. But, will it be the "correct" solution for all values of the relevant constraints, such as the ratio  $A/B$ ?

What we have to require from the correct solution is that it is stable with respect to fluctuations. If we start with the initial concentrations

$$X_i + x, \quad \text{for } t = 0, \quad (1.9)$$

when  $x$  is considered as small, we have to show that

$$x \rightarrow 0, \quad \text{for } t \rightarrow \infty. \quad (1.10)$$

In equilibrium thermodynamics or in the linear range of non-equilibrium thermodynamics such calculations are generally not necessary as it is sufficient to show that the relevant thermodynamic potential (e.g. the free-energy (1.1) or the entropy production) is minimum. However usually there exists no potential far from equilibrium and a direct proof of (1.10) based on stability theory has to be given. Such calculations are standard in hydrodynamics [4], and we shall see some examples for chemical systems later.

The occurrence of dissipative structures is associated with the existence of instabilities at which one branch of the kinetic equations (such as  $X_1$ ,  $M_1$  in the example above) becomes unstable and is replaced by a new branch. It is therefore immediately clear that dissipative structures may only exist in non-linear systems for which more than one solution of the kinetic equations exist.

Moreover dissipative structures will only occur at "finite-distance" from thermodynamic equilibrium as the stability of the "thermodynamic" solution must extend over at least some non-equilibrium region. In fact we shall show in § 4 that instabilities can only occur outside the range of linear thermodynamics of irreversible processes.

The appearance of a dissipative structure may be visualized in phase space in a way very similar to that used to visualize the appearance of an equilibrium structure.

In figs. 1a and 1b, we represent in a schematic way the phase space associated with the liquid and the solid phase (if we consider isothermal systems one has to weight each volume element by the corresponding Boltzmann factor  $\exp(-E/kT)$ ). For temperatures  $T$  above the melting temperature  $T_m$  the phase space associated with the liquid is larger than that associated with the solid. The inverse is true for  $T < T_m$ .

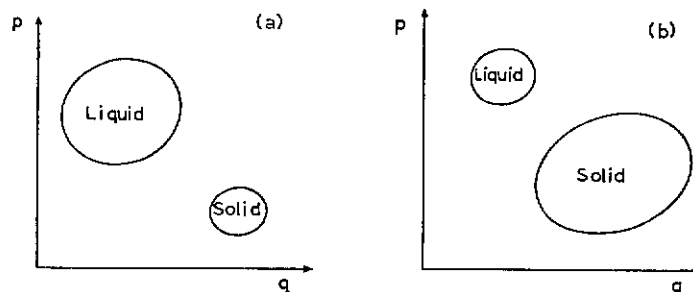


Fig. 1. (a):  $T > T_m$ ; (b):  $T < T_m$ .

Similarly let us suppose that there are two meaningful branches of the kinetic equations (that is such that the corresponding steady state concentrations are real, positive numbers). One of them is what we called the thermodynamic solution stable at equilibrium. As this solution corresponds to a maximum of entropy (or to a minimum of free-energy) it corresponds in the neighborhood of equilibrium to the biggest phase volume (see fig. 2a). If there is an instability it may still have the biggest phase volume but the stable solution is now on the second branch (see fig. 2b). The corresponding loss of phase volume then expresses the appearance of a dissipative structure.

Our main interest will be centered in this report on the specific class of instabilities which are symmetry breaking in the sense that they lead from a homo-

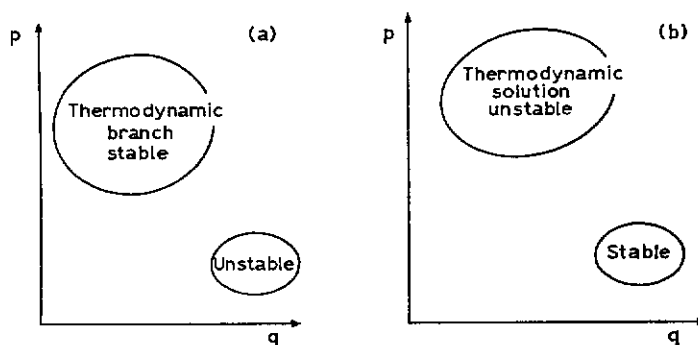


Fig. 2. Phase volumes corresponding to two branches of kinetic equations; (a): below the instability, (b): above the instability.

geneous system to an inhomogeneous one involving both structural and functional order.

We shall also devote some attention to the occurrence of time-order (biological clocks) in dissipative systems. As we shall see there is remarkable parallelism between the problems of structural dissipative order and time-order. Both will appear as possible consequences of large deviations from thermodynamic equilibrium in chemical systems undergoing chemical transformations of essentially the same type.

## 2. Entropy production and stability of equilibrium

As an introduction to the problem of stability of non-equilibrium steady states let us briefly consider the stability of equilibrium states with respect to small perturbations. We shall use a method based on the behavior of entropy production (for more detail see [5]). As is well known, the change of the entropy can be split into two parts. Denoting by  $d_e S$  the flow of entropy due to interactions with the exterior and by  $d_i S$  the entropy production inside the system we have

$$dS = d_e S + d_i S, \quad d_i S \geq 0,$$

or

$$\frac{dS}{dt} = \frac{d_e S}{dt} + \frac{d_i S}{dt}. \quad (2.1)$$

In the macroscopic range (validity of the Gibbs formula), we have

$$\frac{d_i S}{dt} = \int dV \sigma = \sum_i \int dV J_i X_i \geq 0. \quad (2.2)$$

Here  $\sigma$  is the entropy production per unit time and unit volume. Moreover  $J_i$  and  $X_i$  are the flows (or rates) of the irreversible processes and the corresponding

generalized forces (for more detail see [3, 6]). In the case of chemical reactions we have

$$J_i = V_i, \quad (2.3a)$$

$$X_i = \frac{A_i}{T} = - \sum_{\gamma} \frac{\nu_{\gamma i} \mu_{\gamma}}{T}, \quad (2.3b)$$

where  $V_i$  is the reaction rate and  $A_i$  the corresponding affinity related to the chemical potentials  $\mu_{\gamma}$  through the second equality (2.3b). (Also  $\nu_{\gamma i}$  is the stoichiometric coefficient of component  $\gamma$  in reaction  $i$ .)

Similarly in the case of thermal conduction we have

$$\begin{aligned} J &= \mathbf{W}, \\ \mathbf{X} &= \text{grad } (1/T), \end{aligned} \quad (2.4)$$

where  $\mathbf{W}$  is the heat flow.

For chemical reactions we may also write

$$d_i S = \frac{1}{T} \sum_{i=1}^r A_i d\xi_i > 0, \quad (2.5)$$

where  $d\xi_i$  is the change in the extent of reaction as has been defined by De Donder. We shall be mainly interested in the case of chemical reaction. It is well known that a formula such as (2.5) is only valid when the reactions are slow enough so that the collisions restore near equilibrium energy distribution functions [3, 6]. This condition is well met in dense media and we shall therefore assume its validity.

Let us use (2.5) to study chemical equilibrium and stability. At equilibrium we require  $\delta_i S = 0$  for all independent variations of  $\delta\xi_i$ .

$$\delta_i S = \frac{1}{T} \sum_{i=1}^r A_i \delta\xi_i = 0. \quad (2.6)$$

This leads to

$$A_i = - \sum_{\gamma} \nu_{\gamma i} \mu_{\gamma} = 0, \quad i = 1, \dots, r. \quad (2.7)$$

These are the well-known Gibbs conditions for chemical equilibrium. Moreover this equilibrium can only be stable if a spontaneous change (that is satisfying inequality 2.5) is impossible starting from equilibrium. In other words, for each possible change  $\delta\xi_i$  starting from equilibrium we have to require

$$\delta_i S < 0, \quad (2.8)$$

or expanding  $A_i$  around the equilibrium state and using (2.7)

$$\sum_i A_i \delta\xi_i = \sum_i \delta A_i \delta\xi_i < 0. \quad (2.9)$$



If this inequality is satisfied the changes  $\delta\xi_i$  will correspond to *fluctuations* which give rise to a negative entropy production and the equilibrium state will be stable. These conditions are well known. At constant pressure and temperature they imply that the quadratic form [5].

$$\sum_{ij} \left( \frac{\partial A_i}{\partial \xi_j} \right)_{\mu T} \delta\xi_i \delta\xi_j < 0 \quad (2.10)$$

is negative definite. Now let us consider the inequality

$$\sum_{\gamma'} \left( \frac{\partial \mu_\gamma}{\partial n_{\gamma'}} \right)_{\mu T} \delta n_\gamma \delta n_{\gamma'} > 0. \quad (2.11)$$

This condition on chemical potentials is the so-called *stability condition with respect to diffusion* first established by Gibbs [5]. It expresses the statement that any fluctuation of composition which may appear in an initially homogeneous system will be followed by a response which will tend to restore the homogeneity. It is easy to verify that (2.11) implies (2.10). Therefore *stability with respect to diffusion implies stability of chemical equilibrium*. This is a theorem due to Duhem and Jouguet (see ref. [5]).

We shall see that even for steady states the Duhem–Jouguet theorem holds when the steady states are near equilibrium but that it fails for steady states far from equilibrium. This as we shall see is an essential point for the very existence of chemical instabilities.

Besides the diffusion stability condition there exist also stability conditions with respect to thermal and mechanical disturbances which are also used in the theorems we shall discuss in § 3.

Let us now show that these thermodynamic definitions of stability coincide with the kinetic stability conditions introduced in (1.9)–(1.10). Near equilibrium we may write the linear equations

$$\frac{d\delta\xi_i}{dt} = \sum_{i'=1}^r \alpha_{ii'} \delta\xi_{i'}. \quad (2.12)$$

Stability means that the eigenvalues  $\omega$  of this system corresponding to the normal modes have a negative real part. Therefore if we write

$$\delta\xi_i = (\delta\xi_i)_0 e^{\omega t} \quad (\omega = \omega_r + i\omega_i) \quad (2.13)$$

the determinant

$$|\omega\delta_{ii'} - \alpha_{ii'}| = 0 \quad (2.14)$$

has to lead to roots such that for all of them

$$\omega_r < 0. \quad (2.15)$$

The equation (2.14) is called the dispersion equation. Let us first consider the case of real roots. Then

$$\omega = \omega_r, \quad \omega_i = 0. \quad (2.16)$$

The inequality (2.2) together with (2.13) implies

$$\frac{d_i S}{dt} = \sum_i A_i \frac{d\xi_i}{dt} = \omega_r \sum_i A_i \delta\xi_i \geq 0. \quad (2.17)$$

Therefore the thermodynamic stability condition (2.9) indeed leads to the kinetic conditions (2.15) and vice-versa. Let us extend our discussion to the case of complex roots. We then have (the star means complex conjugate)

$$\begin{aligned} \frac{d_i S}{dt} &= \sum_i \left( A_i \frac{d}{dt} (\delta\xi_i)^* + A_i^* \frac{d}{dt} (\delta\xi_i) \right) \\ &= \omega_r \sum_i (\delta A_i \delta\xi_i^* + \delta A_i^* \delta\xi_i) + i\omega_i \sum_i (\delta A_i^* \delta\xi_i - \delta A_i \delta\xi_i^*) > 0. \end{aligned} \quad (2.18)$$

The entropy production is in this way split into two parts, one is associated with the "radial" motion towards the unperturbed state and the other with the rotation around the unperturbed state. In the case studied here where the unperturbed state is an equilibrium state the second term vanishes as a consequence of the symmetry relation

$$\frac{\partial A_i}{\partial \xi_0} = \frac{\partial A_0}{\partial \xi_i}, \quad (2.19)$$

which follows from the relations between affinities and chemical potentials (2.3b). There could therefore be only "reversible", non entropy producing rotations around equilibrium. But even this is excluded, as Balescu and I proved [3] already some years ago that rotations are impossible in the linear range of thermodynamic of irreversible processes as a consequence of the Onsager's reciprocity relations (see 4.2). Rotational motions become only possible in the non-linear range of irreversible processes. We shall come back to this later.

### 3. Evolution criterion and stability of steady states [9]

Let us study in more detail the time variation of the entropy production. Using the notation (2.2) (when not essential, we suppress the integration symbol over the volume) we obtain

$$P = \frac{d_i S}{dt} = \sum_i J_i X_i \geq 0. \quad (3.1)$$

We now decompose the time change  $dP$  of  $P$  into two parts: One is related to the

change of the forces and the other to that of the flows. We therefore have by definition

$$dP = d_X P + d_J P = \sum_i J_i dX_i + \sum_i X_i dJ_i. \quad (3.2)$$

Glansdorff and I proved [3, 7, 8] that for time-independent boundary conditions

$$d_X P = \sum_i J_i dX_i < 0. \quad (3.3)$$

The proof is based on the stability conditions we have enumerated in § 2. As a special case we have for chemical reactions

$$T d_X P = \sum_i V_i dA_i < 0. \quad (3.4)$$

An important feature of (3.3) is the possibility of extending it to include flow processes such as convection [8, 9]. Therefore there exists a quantity  $d\Phi$  of the form

$$d\Phi = \int dV \sum_i J_i' dX_i' < 0, \quad (3.5)$$

where the forces  $X_i'$  and the flows  $J_i'$  now include mechanical processes such as convection terms (see the example § 5). As we then in general deal with inhomogeneous systems we have written (3.5) as a volume integral.

The inequality (3.5) is so general that it can be really called a "universal" evolution criterion of macroscopic physics. However  $d\Phi$  is *not* in general a total differential [7]. Exactly as equilibrium thermodynamics may be based on the study of entropy production and specially on (2.5), the study of steady states may be based on the evolution criterion (3.5). As an example let us show that we can use the evolution criterion (3.3) for chemical non-equilibrium situations exactly as we used  $d_i S$  as given by (2.5) for chemical equilibrium. At the steady state we must have

$$T \delta_X P = \sum_i V_i \delta A_i = 0, \quad (3.6)$$

for *all independent* variations of the affinities. Let us consider as an example the sequence of reactions (1.4) where again the concentrations of  $A$  and  $B$  are fixed. There are two independent affinities because of the condition

$$A_1 + A_2 = \log \frac{A}{B} = \text{given}, \quad (3.7)$$

or

$$\delta A_1 + \delta A_2 = 0. \quad (3.8)$$

Therefore (3.6) leads to

$$\left. \begin{aligned} V_1 &= V_2, \\ V_3 &= 0, \end{aligned} \right\} \quad (3.9)$$

which are of course the usual steady state conditions and include as a special case the equilibrium conditions

$$V_1 = V_2 = V_3 = 0. \quad (3.10)$$

Again in complete parallelism with the study of equilibrium situations the steady state will be stable if [10]

$$\delta_X P \geq 0, \text{ or } \delta\Phi \geq 0, \quad (3.11)$$

for all perturbations *compatible with the kinetic equations of the system*. In the chemical case this leads using (3.4) and (3.6) to the stability condition

$$T\delta_X P = \sum_i \delta V_i \delta A_i > 0. \quad (3.12)$$

The stability theory of steady states may be conveniently subdivided into two parts:

a) the identification of phenomena which may give rise to *negative* contributions to  $\delta_X P$  or more generally to  $\delta\Phi$  (when hydrodynamic flow phenomena are included),

b) the discussion of the numerical value of such negative terms and specially the discussion of the possibility that the sum involved in (3.11) or (3.12) may become negative *without violating* the kinetic equations.

The first part can at present be treated in a quite general way. We shall see in §§ 5, 6 that mechanical convection as well as certain auto- and crosscatalytic chemical reactions indeed give negative contributions. They are therefore the phenomena which are "dangerous" for the stability and of special interest for us here. The second part involves the solution of the dispersion equation for small perturbations or some approximate method (for example the use of the local potential method, [9]).

In the evolution criterion (3.4) or (3.5) the generalized rates and forces play a quite different role. No inequality for  $\delta_J P$  outside the linear range (see 4.4) is known. It is therefore quite remarkable that in the stability condition (3.11) or (3.12) the rates and forces play again a symmetric rôle. For example in the chemical case the entropy production is

$$T \frac{d_i S}{dt} = \sum_i A_i V_i \geq 0, \quad (3.13)$$

which has to be compared to the quantity (3.12) which determines the stability of the system.

We may therefore also call  $\delta_X P$  or  $\delta\Phi$  the "excess entropy production" (more briefly E.E.P.) near the steady state we consider.

We see therefore that a sufficient condition of stability is that the E.E.P. is positive. In this *very specific sense* we may say that the theorem of minimum entropy production is valid for an arbitrary stable steady state.

Let us now consider a certain number of examples.

#### 4. The linear range of thermodynamics of irreversible processes

Let us introduce the following assumptions:

- a) Linear phenomenological laws

$$J_i = \sum_j L_{ij} X_j. \quad (4.1)$$

- b) Validity of Onsager's reciprocity relations

$$L_{ij} = L_{ji}. \quad (4.2)$$

- c) Phenomenological coefficients  $L_{ij}$  may be treated as constants.  
d) No mechanical flow processes.

Inequality (3.1) then becomes

$$P = \sum_{ij} L_{ij} X_i X_j \geq 0. \quad (4.3)$$

Moreover it can be easily shown that in this range [3]

$$d_X P = d_J P = \frac{1}{2} dP < 0. \quad (4.4)$$

Therefore in the linear domain the entropy production can only decrease and steady states are characterized by a minimum of entropy production [3].

Moreover it is clear that such steady states are automatically stable. Indeed in the neighborhood of the steady state we have (see 3.12, 4.1 and 4.3)

$$\delta_X P = \sum_i \delta J_i \delta X_i = \sum_{ij} L_{ij} \delta X_i \delta X_j \geq 0. \quad (4.5)$$

Note that we have here for the perturbation of the entropy production near the steady state valid till second order,

$$\delta P = \sum_i J_i^0 \delta X_i + \sum_i X_i^0 \delta J_i + \sum_i \delta J_i \delta X_i. \quad (4.6)$$

Here  $J_i^0$  and  $X_i^0$  are the flows and forces at the steady state. We have also used (3.6) (see also (4.4)). Therefore we have near the steady state including terms of second order

$$\delta_X P = \frac{1}{2} \delta P \geq 0. \quad (4.7)$$

As we see the positive sign of  $\delta_X P$  is related to the theorem of minimum of entropy production. This sign shows that the stability criterion (3.11) is automatically satisfied. No instabilities may arise in the linear range.

To understand this result we have to remember that inequalities (3.3) and (3.5) are based on the validity of the stability conditions for equilibrium. Our result (4.5) simply indicates that once the *equilibrium* is stable, *steady states* in the neighborhood of equilibrium are automatically stable as well. Using the terminology

of § 1 we could say that the "thermodynamic solution" of the kinetic equations may be continued at least in some neighborhood of equilibrium.

Specifically for chemical reactions we may state that the Jouguet-Duhem theorem mentioned in § 2 includes not only chemical equilibria but also the whole range of steady states which belong to the linear range of non-equilibrium thermodynamics.

This shows that the problem of occurrences of new dissipative structures is outside the range of the theorem of minimum entropy production. This theorem only describes steady states which may be obtained through a continuous "deformation" of the equilibrium situation.

### 5. Hydrodynamic instabilities

The case of hydrodynamic instabilities has been treated in the frame of this method by Glansdorff [8, 9]. We include here a brief summary in order to be able to compare hydrodynamic and chemical instabilities.

To be specific let us consider a two-dimensional laminar flow at constant temperature between two parallel walls. We have here (*see* 3.5)

$$\left. \begin{aligned} J' &= -(\mathbf{P} + \rho \mathbf{v} \mathbf{v}), \\ \mathbf{X}' &= \frac{1}{T} \frac{\partial \mathbf{v}}{\partial \mathbf{x}}, \end{aligned} \right\} \quad (5.1)$$

where  $\mathbf{P}$  is the pressure tensor,  $\mathbf{v}$  the convection velocity. The force  $\mathbf{X}'$  is purely dissipative, but the corresponding flow has now besides the usual dissipative contribution  $\mathbf{P}$  related to the viscosity, also a contribution due to convection.

After a few simple manipulations which are described elsewhere one finds [see ref. 9, page 50] in the neighborhood of the laminar flow

$$T \frac{d\Phi}{dt} = \eta N - \rho M, \quad (5.2)$$

with

$$\eta N = \eta \iint y^2 dx dy, \quad y = \frac{\partial v}{\partial x} - \frac{\partial u}{\partial y}, \quad (u = \delta v_x, v = \delta v_y) \quad (5.3)$$

$$\rho M = -\rho \iint uv \frac{\partial v_x^0}{\partial y} dx dy = -\int \rho \langle uv \rangle \frac{\partial v_x^0}{\partial y} dy. \quad (5.4)$$

Therefore  $\eta N$  represents the viscous dissipation and  $\rho M$  the conversion of energy from the basic into the disturbance by a Reynolds shear.

The contribution of the viscosity to (5.2) is always positive. If we could neglect the inertial contribution  $\rho M$  we would always have a stable laminar regime.

On the contrary, the inertial term  $\rho M$  has no definite sign. Instability may occur if  $\rho M$  is positive and can compensate the dissipative term  $\eta N$ .

The relative magnitude of these two terms may be written in the form

$$\frac{\rho M}{\eta N} = R \frac{M'}{N'}, \quad (5.5)$$

where  $R$  denotes the Reynolds number and  $M'$ ,  $N'$  are dimensionless forms of  $M$  and  $N$ .

Instability of the laminar flow will occur for  $M > 0$  and for a Reynolds number larger than the critical value

$$R_c = \frac{N'}{M'}. \quad (5.6)$$

Then the transfer of kinetic energy into the fluctuations will exceed the decrease of kinetic energy due to viscosity and turbulence will occur.

These considerations are well known (for the references to the papers by Orr, Dryden, Murnaghan and Bateman, see [9]). We only wanted to show that we have here a special case of our general evolution criterion (3.5). It should be noticed that in the transition between laminar and turbulent flow the entropy production  $d_1 S/dt$  (due here to viscosity) *increases*. This is also true for all other hydrodynamic instabilities such as the Bénard and Taylor instabilities.

As a result (see 2.1) in the steady state when  $d_1 S/dt = 0$ , (at least in an average sense if there are time-oscillations) the entropy flow  $d_e S/dt$  increases in absolute value.

The dissipative structure involved in hydrodynamic instabilities has therefore a simple thermodynamic meaning: it appears as a response of the system to non-equilibrium conditions and leads to a more efficient mechanism for restoring equilibrium in the system as a whole.

## 6. Chemical instabilities

The basic quantity we have to consider is according to (3.12)

$$T \delta_X P = \sum_i \delta V_i \delta A_i. \quad (6.1)$$

Instabilities may only occur if at least some terms in this sum are negative. Such terms would then play the role of the convection terms such as  $\rho M$  we have considered in hydrodynamics.

Let us consider the chemical reaction



As we are now mainly interested in far from equilibrium situations we neglect

the reverse reaction and write for the reaction rate (we again take equal to one all kinetic and equilibrium constants as well as  $RT$ )

$$V = XY. \quad (6.3)$$

The affinity is

$$A = \log \frac{XY}{CD}. \quad (6.4)$$

A fluctuation in the concentration  $X$  around some steady state value gives rise to an excess entropy production

$$\delta V \delta A = \frac{Y}{X} (\delta X)^2 > 0. \quad (6.5)$$

Such a fluctuation would therefore not bring into danger the stability condition (3.12).

Let us now consider instead of (6.4) the autocatalytic reaction



The reaction rate is still assumed to be given by (6.3), but the affinity is now

$$A = \log \frac{XY}{X^2} = \log \frac{Y}{X}. \quad (6.7)$$

We have now a "dangerous" contribution to the excess entropy production. Detailed calculations given in § 7 will show that indeed under well defined conditions such autocatalytic reactions give rise to instabilities and dissipative structures.

Of course (6.6) is meant here only as an example. As we shall see later there may be more subtle ways involving fluctuations of more than one component to produce negative contributions to the E.E.P.

Before we go to the study of specific examples we want to present the following observation. There are at least two types of chemical instabilities:

- a) instabilities in respect to homogeneous perturbations;
- b) instabilities in respect to space-dependent inhomogeneous perturbations;

In case a) we expect the system to go from a homogeneous steady state to another homogeneous state (which may be steady or not). In case b) diffusion plays an essential role. Diffusion appears in this theory in a twofold way:

- 1) it gives a *positive* contribution to the E.E.P. similar to that of viscous dissipation in hydrodynamics (5.2); this effect can only *stabilize* the steady state;
- 2) it increases the manifold of perturbations compatible with the macroscopic

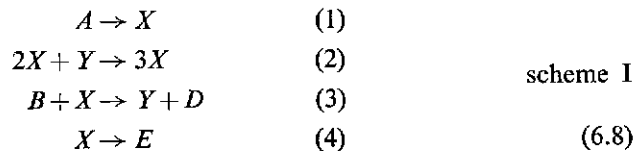


equations of change (the kinetic equations). We have to test the stability of the system with respect to a wider class of situations.

If the second effect is dominant we may expect instabilities with respect to inhomogeneous perturbations and the appearance of new states which are no longer homogeneous in space.

We have then "symmetry breaking" instabilities [12] which, we believe are especially important from the point of view of the interpretation of biological order.

Let us now consider some explicit examples. A very simple scheme of reactions which may give rise to instabilities is the following



The overall reaction is



This reaction scheme is physically unrealistic because it involves the trimolecular step (2). We shall indicate below other schemes which do not involve such a step. But the algebra involved in the discussion of (6.8) is much simpler as it involves only two intermediate components  $X$ ,  $Y$  and for this reason we shall discuss it in more detail and simply quote the results obtained for the other schemes (for more detail see [13]). The kinetic equations are

$$\frac{\partial X}{\partial t} = A + X^2 Y - BX - X + D_X \frac{\partial^2 X}{\partial r^2}, \quad (6.10)$$

$$\frac{\partial Y}{\partial t} = BX - X^2 Y + D_Y \frac{\partial^2 Y}{\partial r^2}. \quad (6.11)$$

As usual we maintain constant the concentrations of the initial and the final components  $A$ ,  $B$ ,  $D$ ,  $E$ . The reverse reactions are neglected. The value of the non-vanishing kinetic constants is taken equal to one. We take into account diffusion. To simplify we assume a one-dimensional medium. There exists always a time-independent homogeneous solution

$$X_0 = A, \quad Y_0 = \frac{B}{A}. \quad (6.12)$$

This is the continuation of the thermodynamic solution (see § 1). To investigate its stability we first investigate the dispersion equation (see 2.14). We consider perturbations of the form

$$\left. \begin{aligned} X &= X_0 + x e^{(\omega t + i r/\lambda)}, \\ Y &= Y_0 + y e^{(\omega t + i r/\lambda)}, \end{aligned} \right\} \quad (6.13)$$

with

$$\left| \frac{x}{X_0} \right| \ll 1, \quad \left| \frac{y}{Y_0} \right| \ll 1.$$

Inserting (6.13) into (6.10) and (6.11) we obtain

$$\left. \begin{aligned} (\omega - B + 1 + a)x - A^2 y &= 0, \\ Bx + (\omega + A^2 + b)y &= 0, \end{aligned} \right\} \quad (6.14)$$

with

$$a = \frac{D_X}{\lambda^2}, \quad b = \frac{D_Y}{\lambda^2}. \quad (6.15)$$

The corresponding dispersion equation is

$$\omega^2 + (A^2 + 1 - B + a + b)\omega + A^2(1 + a) + (1 - B)b + ab = 0. \quad (6.16)$$

There exists a critical value

$$B_c(\lambda) = \frac{1}{b}(1 + a)(A^2 + b), \quad (6.17)$$

which separates a root  $\omega < 0$  from a root  $\omega > 0$ . We now have to look for the critical value of the wave length  $\lambda_c$  at which the instability begins. To do this we have to calculate the wave length which gives to (6.17) its minimum value. This leads immediately to

$$(\lambda_c)^2 = \frac{1}{A}(D_X D_Y)^{\frac{1}{2}} \quad (6.18)$$

and substitution in (6.17) gives

$$B_c = \left[ A \left( \frac{D_X}{D_Y} \right)^{\frac{1}{2}} + 1 \right]^2. \quad (6.19)$$

To discuss these expressions it is useful to repeat the calculations without putting the kinetic coefficients equal to one. If we call  $k_i$  the kinetic coefficient corresponding to step  $i$  in (6.9) we obtain

$$\lambda_c^2 = \left( \frac{k_4}{k_1^2 k_2} \right)^{\frac{1}{2}} \frac{(D_X D_Y)^{\frac{1}{2}}}{A} \quad (6.18')$$

and

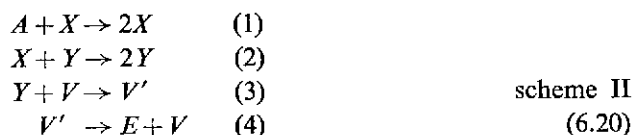
$$B_c = \left[ \frac{k_1}{k_4} \left( \frac{k_2 D_X}{k_3 D_Y} \right)^{\frac{1}{2}} A + \left( \frac{k_4}{k_3} \right)^{\frac{1}{2}} \right]^2. \quad (6.19')$$

We see that  $\lambda_c$  and  $B_c$  depend in an intrinsic way on both the various reaction rates and on the diffusion constants. If diffusion as compared to reaction rates

becomes small, instability occurs for short wave length perturbations. In the inverse case the instability occurs for long wave lengths. This is quite reasonable and we shall come back to this point below.

We see that we have here a symmetry breaking instability as the system beyond the instability can no longer be expected to be homogeneous. We shall study this question in greater detail in § 7.

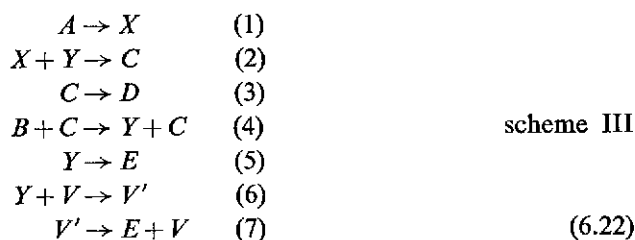
Let us indicate three other reaction schemes which also may lead to chemical symmetry-breaking instabilities:



The overall reaction is



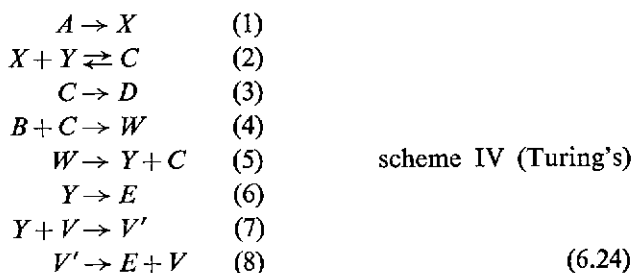
There are only one- and two-molecular steps. In this scheme both  $X$  and  $Y$  catalyze their own formation. It is a modification of a scheme suggested by Lotka [14] to investigate chemical oscillations (we discuss Lotka's scheme in § 8). We have simply added the "appendix" (3)–(4) involving the intermediate compound  $V'$ . Such an appendix also plays a role in the next schemes, such as



This is a simplified form of Turing's original scheme [11] (see also [12]). We have the two overall reactions

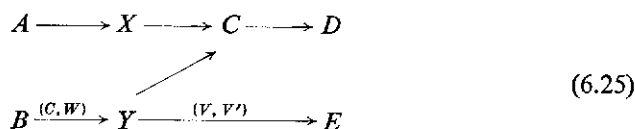


Let us finally indicate Turing's scheme



The Turing scheme IV differs from III only by the presence of the intermediate component  $W$ . Also the step (2) is supposed to be reversible. In an earlier paper [12] this scheme has been studied in great detail and it has been shown that in agreement with our general conclusion of § 4 no instability can occur when the affinities of the overall reactions (6.23) are smaller than some critical values.

One may broadly describe schemes III and IV by saying that the initial products  $A, B$  are transformed into the final (or "waste") products  $D$  and  $E$  through the intermediate products  $X, Y$  and by the action of the catalysts  $C, V, V', W$  following the general scheme



Let us now consider the thermodynamic aspects of the chemical instability in terms of the basic quantity (6.1). We again go into more detail for the reaction scheme I. Using the kinetic equation (see (6.10, 11)) we find for (6.1), including the effect of diffusion

$$\delta_x P = (1-B) \frac{x^2}{A} + \frac{A^2}{B} y^2 + \frac{a}{A} x^2 + \frac{bA}{B} y^2. \tag{6.26}$$

Two interesting remarks have to be made:

1) in agreement with our general discussion there appears in the E.E.P. (6.26) the negative term  $-Bx^2/A$  due to the autocatalytic action of  $x$ ; this is the "dangerous" contribution we have mentioned earlier;

2) the explicit contribution of diffusion to the E.E.P. is positive and proportional to  $D/\lambda^2$  (the last two terms in 6.26). Therefore if there is an instability, increasing values of  $D$  must give rise to increasing values of the critical wave length. If not, the contribution of diffusion to (6.26) would become dominant and  $\delta_x P$  would be always positive. This is in agreement with the formula for  $\lambda_c$  (6.18) derived from the dispersion equation. But the diffusion has as we already mentioned a second role: the manifold of perturbations which we may introduce into (6.26) is now increased by the consideration of inhomogeneous systems. Let us verify that indeed the perturbations  $(x, y)$  which satisfy (6.14) at the marginal state  $\omega=0$  lead to the vanishing of the E.E.P. Indeed we first obtain using (6.14) and (6.17)

$$y = -\frac{(1+a)}{b} x. \tag{6.27}$$

If we now substitute in (6.26) and again use (6.19) we obtain indeed

$$(\delta_x P)_{B=B_c} = 0. \tag{6.28}$$

There is therefore complete agreement between the *kinetic theory of chemical instabilities based on the dispersion equation and the thermodynamic theory developed in § 3.*

The situation for the reaction scheme II described in (6.25) is quite similar. The autocatalytic character of  $X$ ,  $Y$  again introduces negative terms into the E.E.P. It is interesting to comment briefly on the role of the appendix (steps 3 and 4 in 6.25). It appears that its role is quite similar to that of diffusion (for more details see [13]): it gives a positive contribution to the E.E.P. However at the same time it increases the range of permissible perturbations. Instability appears if the steady state concentration of  $V'$  is larger than some critical value.

The schemes III and IV again lead to an E.E.P. which contains dangerous contributions. However here the negative terms are of the form ( $\alpha$  is a positive constant)

$$-\alpha y c \quad (6.29)$$

and *not*

$$-\frac{B}{A} x^2, \quad (6.30)$$

as in (6.26). This is quite natural as we have in these schemes a *crosscatalytic* effect:  $Y$  catalyzes the formation of  $C$  and inversely  $C$  the formation of  $Y$ .

We believe that the situation for chemical instabilities as compared to that described in our earlier paper [12] has been greatly clarified. We see indeed that:

- 1) there are many reaction schemes which may lead to chemical instabilities; in fact it would be easy to imagine others than those we have listed;
- 2) they are all characterized by negative contributions to the E.E.P. due to autocatalytic or crosscatalytic effects;
- 3) the essential and unexpected role of diffusion is clearly understood.

Let us now consider the physical situation beyond the chemical instability point.

## 7. Chemical dissipative structure

The study of the time evolution of the steady states beyond an instability is always rather lengthy and difficult [11]. Again scheme I studied in § 6 provides us with a relatively simple example [13].

However instead of considering disturbances of arbitrary wave length  $\lambda$  we shall now consider a system of two boxes. On the contrary the concentrations of  $X$  and  $Y$  may be different. Instead of (6.10, 11) we now have the four equations

$$\left. \begin{aligned}
 \frac{dX_1}{dt} &= A + X_1^2 Y_1 - BX_1 - X_1 + D_X(X_2 - X_1), \\
 \frac{dX_2}{dt} &= A + X_2^2 Y_2 - BX_2 - X_2 + D_X(X_1 - X_2), \\
 \frac{dY_1}{dt} &= BX_1 - X_1^2 Y_1 + D_Y(Y_2 - Y_1), \\
 \frac{dY_2}{dt} &= BX_2 - X_2^2 Y_2 + D_Y(Y_1 - Y_2).
 \end{aligned} \right\} \quad (7.1)$$

As in (6.12) we have a single time-independent homogeneous solution

$$X_i = A, \quad Y_i = \frac{B}{A} \quad (i=1, 2). \quad (7.2)$$

We now want to study the stability of this solution in respect to solutions in which the two boxes have different compositions. Let us write

$$\left. \begin{aligned}
 X_2 - X_1 &= x e^{\omega t}, \\
 Y_2 - Y_1 &= y e^{\omega t}.
 \end{aligned} \right\} \quad (7.3)$$

We again obtain a second order dispersion equation (see 6.16)

$$\omega^2 + (1 + A^2 + 2D_X + 2D_Y - B)\omega + A^2(1 + 2D_X) + 2D_Y + 4D_X D_Y - 2BD_Y = 0. \quad (7.4)$$

This leads to the critical value

$$B_c = \frac{1}{2D_Y} (A^2 + 2D_X A^2 + 2D_Y + 4D_X D_Y). \quad (7.5)$$

The basic difference from (6.19) is that here instability arises only for a finite range of values of the diffusion coefficients. Both for

$$D_X, D_Y \rightarrow 0 \quad (7.6)$$

and for

$$D_X, D_Y \rightarrow \infty, \quad (7.7)$$

we have

$$B_c \rightarrow \infty. \quad (7.8)$$

This is clearly related to the fact that the wavelength is here artificially imposed by the size of the system.

To continue the calculations we make the following choice of numerical values

$$A = 2, \quad D_X = D_Y = 1, \quad (7.9)$$

therefore

$$B_c = 9. \quad (7.10)$$

After a few simple manipulations the time-independent solutions of (7.1) are shown to satisfy the equations

$$\left. \begin{aligned} -3X_2^5 + 30X_2^4 - (2B + 102)X_2^3 + (12B + 132)X_2^2 \\ - (16B + 96)X_2 + 96 = 0 \quad (1) \\ X_1 = 4 - X_2 \quad (2) \\ Y_2 = \frac{1}{X_2} \left( B + 3 - \frac{6}{X_2} \right) \quad (3) \\ Y_1 = Y_2 + X_2^2 Y_2 - BX_2 \quad (4) \end{aligned} \right\} \quad (7.11)$$

We have therefore to solve the fifth order equation (1) and to replace  $X_2$  by its value in the other equations. This can of course be done easily using standard methods of numerical calculation.

The results are the following:

a) for  $B < B_c$  equation (1) has only one real root

$$X_2 = 2. \quad (7.12)$$

This is the homogeneous solution (see 7.2). All other roots are complex and therefore devoid of physical meaning;

b) for  $B > B_c$  equation (1) has three real roots:

- 1) the homogeneous solution (7.12);
- 2) an inhomogeneous solution;
- 3) an inhomogeneous solution obtained by permutation of  $X_2$  with  $X_1$ .

On fig. 3 we have represented the homogeneous and inhomogeneous roots above the critical point.

We have here a striking case of a dissipative structure as defined in the introduction.

In one compartment say 2 the concentration of  $Y$  is larger than in the other, at the same time  $X$  is smaller. If we refer to the reaction scheme (6.8) we see that the consumption of  $B$  will essentially proceed in compartment 1. The system begins to look like a kind of "factory" with characteristic structural and functional order.

The stability of the dissipative structure may in turn be analyzed using equations (7.1). The study of the corresponding dispersion equations indicates that it is stable for

$$9.8 < B < 11.2. \quad (7.13)$$

Outside this range at least one root of the dispersion equation has a positive real part.

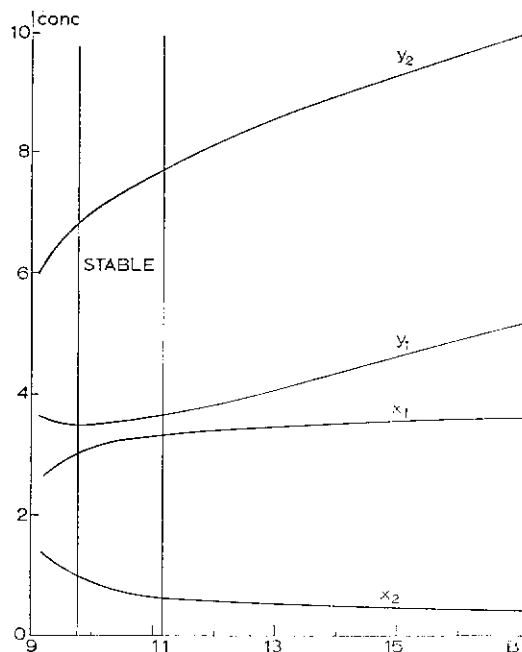


Fig. 3. Steady States for systems (7.1) beyond the critical point (for the numerical values adopted see text).

We don't know yet what happens there: it seems likely to us that this instability arises from the artificial division of the systems into two homogeneous boxes. The real steady state may correspond to a much more complicated distribution of matter.

Certainly the behavior of matter beyond the instability deserves a much more careful investigation (specially as we are not able to reproduce some of the results given in Turing's paper [11]). However the existence of dissipative structures arising beyond symmetry breaking chemical instabilities seems to us established with a reasonable degree of certitude.

## 8. Chemical oscillations

The last paragraphs were mainly devoted to the study of structural order. Let us now consider the problem of order in time and specially the problem of oscillations around steady states. We go back to our general evolution criterion (3.4) which we write in the neighborhood of the steady state (see also 2.18)

$$T \frac{d_x P}{dt} = \frac{1}{2} \sum_i \left( \delta V_i^* \frac{d \delta A_i}{dt} + \delta V_i \frac{d \delta A_i^*}{dt} \right) \leq 0. \quad (8.1)$$



Indeed we now have to consider complex normal modes. We obtain exactly as in (2.18)

$$T \frac{dX^P}{dt} = \omega_r \frac{1}{2} \sum_i (\delta V_i^* \delta A_i + \delta V_i \delta A_i^*) + i\omega_i \frac{1}{2} \sum_i (dV_i^* \delta A_i - \delta V_i dA_i^*) < 0. \quad (8.2)$$

The first term in (8.2) may be associated with the approach to the steady state, the second with the rotation around the steady state. Now it is easy to see that equilibrium stability conditions imply that each of these terms is *separately* negative (see also [27]). Indeed (see 2.3b)

$$\delta A_i = - \sum_{\gamma'} v_{\gamma i} \frac{\partial \mu_\gamma}{\partial n_{\gamma'}} \delta n_{\gamma'},$$

$$\frac{dn_\gamma}{dt} = \sum_i v_{\gamma i} V_i, \quad \frac{d\delta n_\gamma}{dt} = \sum_i v_{\gamma i} \delta V_i. \quad (8.3)$$

Therefore we obtain

$$\begin{aligned} \omega_r \sum_i (\delta V_i^* \delta A_i + \delta V_i \delta A_i^*) &= -\omega_r \sum_{\gamma'} \frac{\partial \mu_\gamma}{\partial n_{\gamma'}} \left( \frac{d\delta n_\gamma^*}{dt} \delta n_{\gamma'} + \frac{d\delta n_\gamma}{dt} \delta n_{\gamma'}^* \right) \\ &= -\omega_r^2 \sum_{\gamma'} \frac{\partial \mu_\gamma}{\partial n_{\gamma'}} (\delta n_\gamma^* \delta n_{\gamma'} + \delta n_\gamma \delta n_{\gamma'}^*) < 0, \end{aligned} \quad (8.4)$$

where we used the stability condition (2.11). In the same way it is easy to prove that the second term in (8.2) is separately negative.

We have therefore two inequalities, the first is the same as we discussed in connexion with the stability of steady states, the second gives us the *direction of rotation* around the steady state (see also [3]).

Very little is known about the general conditions for the appearance of rotations. We have already quoted in § 2 our theorem [3] that rotations can appear only far from equilibrium. Also Bak [15] and others have proved that rotations cannot appear for reaction schemes involving only monomolecular reactions.

Our evolution criterion (8.2) shows that rotations are only possible if

$$\sum_i (\delta V_i^* \delta A_i - \delta V_i \delta A_i^*) \neq 0. \quad (8.5)$$

A necessary and sufficient condition is that the matrix which relates, near the steady state, the rates  $\delta v_i$  to the affinities  $\delta A_j$ , is not symmetric.

Indeed let us write

$$\delta V_i = \sum_j L_{ij} \delta A_j = \frac{1}{2} \sum_j L_{(ij)} \delta A_j + \frac{1}{2} \sum_j L_{[ij]} \delta A_j, \quad (8.6)$$

with

$$L_{(ij)} = L_{ij} + L_{ji}, \quad L_{[ij]} = L_{ij} - L_{ji}. \quad (8.7)$$

Indeed (8.5) may be written (the  $L_{ij}$  are real)

$$\sum_{ij} L_{[ij]} \delta A_j^* \delta A_i \quad (8.8)$$

and vanishes when  $L_{ij}$  is a symmetric matrix. However it is not easy to use this criterion to discuss the mechanisms which give rise to rotations.

When the system presents pure, undamped rotations the first term in (8.2) has to vanish

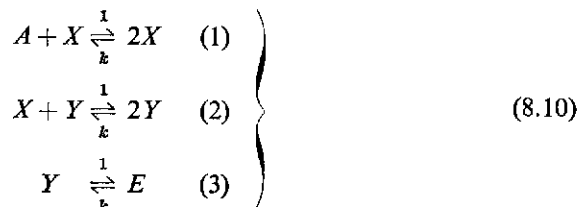
$$\sum_i (\delta V_i^* \delta A_i + \delta V_i \delta A_i^*) = 0. \quad (8.9)$$

This condition is very similar to that used in the stability theory (see §§ 4, 6): it can only be satisfied if there appear negative contributions to the excess entropy production. Therefore most of our discussions of § 6 apply as well to the problem of rotations. It is necessary to have steps involving autocatalytic or crosscatalytic reactions. This is in complete agreement with the conclusions reached by Chance and his coworkers [16, 17].

In fact all the schemes we discussed in § 6 lead for some range of the constraints involved to rotations. However the inverse is not true: even undamped rotations may occur on the thermodynamic branch and are not necessarily related to instabilities.

To illustrate these conclusions, let us consider two simple examples [18].

We first consider the autocatalytic Lotka-process [14]



The difference from (6.20) is that here we have suppressed the "appendix" involving  $V'$  which is necessary to obtain a chemical instability. As before we put all *direct* kinetic constants equal to one. However we do not neglect the inverse kinetic constants which we put equal to  $k$ . In this way we may discuss the behavior of (8.10) for all values of the overall affinity. The concentrations of the initial and final products  $A$ ,  $E$  are maintained constant. The overall affinity is

$$\mathcal{A} = \mathcal{A}_1 + \mathcal{A}_2 + \mathcal{A}_3 = RT \log \frac{A}{k^3 E}. \quad (8.11)$$

At thermodynamic equilibrium (total affinity is vanishing)

$$\left( \frac{A}{E} \right)_{\text{eq}} = k^3. \quad (8.12)$$

It is easy to show that the time-independent solutions of the kinetic equations satisfy the equations

$$X_0 = 1 + kY_0 - \frac{kE}{Y_0},$$

$$k^3Y_0^4 + (1 - kA + 2k^2)Y_0^3 + (k - A - kE - 2k^3E)Y_0^2 + (kEA - 2k^2E)Y_0 + k^3E^2 = 0. \quad (8.13)$$

The dispersion equation can also be easily obtained. It is

$$\omega^2 + (Y_0 - X_0 + 2kX_0 + 2kY_0)\omega + X_0 + 2kX_0 - 1 - 2kX_0^2 - 2kY_0 + Y_0 + 4k^2X_0Y_0 = 0. \quad (8.14)$$

Numerical calculations have been performed for

$$k = 10^{-2}, \quad A = 1. \quad (8.15)$$

It has been shown that the thermodynamic solution remains stable for the whole range of values of the total affinity. In addition there exists a critical value of the total affinity corresponding to the appearance of two complex frequencies in the dispersion equation (8.14)

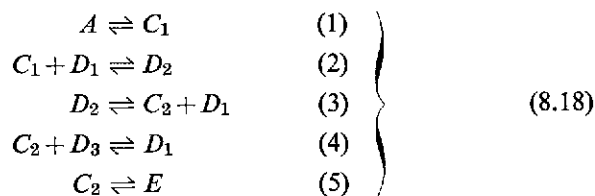
$$\omega = \omega_r \pm i\omega_i, \quad \text{with } \omega_r < 0. \quad (8.16)$$

The critical value of the affinity is

$$\frac{\mathcal{A}_c}{RT} = 9.2. \quad (8.17)$$

In addition if one now takes  $k=0$  (no inverse reactions i.e.  $\mathcal{A} \rightarrow \infty$ ) one finds  $\omega_r=0$ ; one has then pure, undamped rotations.

Similar conclusions may be reached with the glycolytic scheme proposed by Chance and Higgins [17, 18]. We have investigated the following slightly simplified version of this mechanism



Here  $C_1, C_2$  are intermediate compounds and  $D_1, D_2, D_3$  some enzymes. The critical step is the reaction (4) between enzyme  $D_3$  and the substrate  $C_2$  to form the active enzyme  $D_1$  which interacts with  $C_1$ . We have shown that the "thermodynamic solution" is stable over the whole range of the overall affinity  $\mathcal{A}$  and moreover there exists a critical value of  $\mathcal{A}$  above which rotations begin to occur.

These examples which are in agreement with our thermodynamic theory confirm that time-organization is exactly as is dissipative structure a response to far from equilibrium conditions.

### 9. Fluctuations and instabilities

Let us start with the classical Einstein formula [19] based on the Boltzmann principle: the probability of a fluctuation around an equilibrium state is related to the entropy change  $\Delta_i S$  due to the fluctuation by (apart from a normalization constant)

$$P \sim \exp \frac{\Delta_i S}{k}. \quad (9.1)$$

For an isolated system there is no exchange of entropy with the outside world. Therefore

$$\Delta_i S = \Delta S. \quad (9.2)$$

Moreover the entropy is then a maximum and  $\Delta S$  begins with a second order term as

$$\Delta S = \frac{1}{2}(\delta^2 S) + \dots \quad (9.3)$$

When higher order terms may be neglected (9.1) reduces to the Gaussian form

$$P \sim \exp \frac{1}{2k}(\delta^2 S). \quad (9.4)$$

The entropy change  $\delta^2 S$  can easily be calculated (see e.g. [20]). For example in the case of temperature fluctuations one finds

$$\delta^2 S = - \int dV \rho \frac{C_v}{T^2} (\delta T)^2 < 0. \quad (9.5)$$

Because of the thermal stability condition  $C_v > 0$  (see § 1) this expression is definite negative.

As has been indicated elsewhere [20] formula (9.4) may also be used to calculate fluctuations around non-equilibrium steady states. In the case of temperature fluctuations the only difference would be that  $T$  in the denominator of (9.5) would refer to the local temperature  $T(x)$  which is now space-dependent.

We could say that (9.4) provides us with a *thermodynamic definition of fluctuations*. To be consistent we have of course to show that a fluctuation would regress on the average with an *increase*  $-\delta^2 S$  of entropy.

Indeed one may show (see ref. [10]) that

$$\frac{d_1 \delta^2 S}{dt} = - \int dV \delta J \delta X. \quad (9.6)$$

The analogy with (2.2) is striking. The excess entropy production we used to discuss stability theory is precisely the time change of the excess entropy  $\delta^2 S$ . Therefore in the whole range of stability of the thermodynamic solution of the kinetic equations the fluctuations will regress (for time-independent boundary conditions).

The situation changes drastically beyond an instability. The thermodynamic definition (9.4) of a fluctuation is no more valid around the unstable state. The evolution of the system goes spontaneously to situations which are *less probable* from the point of view of the Einstein formula. This is a completely general conclusion valid for all instabilities whatever their origin.

We may say that after the instability the role of the basic structure and of fluctuations are exchanged: what was a fluctuation before now becomes a stable structure maintained through the flow of energy and matter.

## 10. Chemical instabilities and biochemical mechanisms

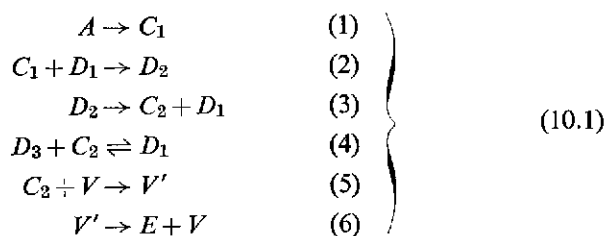
We believe that the discussion presented in the preceding paragraphs establishes firmly the existence of chemical instabilities and consequently of chemical dissipative structures. It may therefore be stated that a theoretical basis exists for the understanding of structural and functional order in chemical systems.

Are these considerations relevant for biological systems? Clearly the answer can only come from biologists. However I would like to present two general arguments in favor of an affirmative answer:

1) the general picture of a dissipative structure as presented for example in § 7 has a striking similarity with the description of biological order as has emerged from the progress in molecular biology [1];

2) the chemical mechanisms considered in molecular biology are often precisely of the type considered in §§ 6-7 and may indeed lead to chemical instabilities.

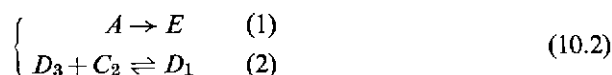
As an example let us discuss in more detail the Chance-Higgins mechanism for oscillatory reactions [13, 16, 17]. This mechanism may be written.



As in (8.18)  $C_1$ ,  $C_2$ , are intermediate compounds,  $D_1$ ,  $D_2$ ,  $D_3$  enzymes,  $A$  the initial compound and  $E$  the final compound. The concentration of  $D_3$  is maintained constant. Here we have two supplementary intermediate compounds  $V$ ,  $V'$ . In the specific case studied by Chance and al. [16, 17]  $A$  is glucose and  $E$  glyceraldehyde phosphate.

As Lefever has shown (the calculation will be given in ref. [13]), this scheme does not lead to chemical instabilities. This can be understood as follows. We have

two resultant reactions



While the reaction (1) is taking place in non-equilibrium conditions (its affinity may be taken as infinite), the reaction (2) may be considered at equilibrium as the steady state conditions lead to

$$V_4 = 0$$

for the rate of step (4) of the scheme (10.1). Now in a similar situation Nicolis and I have shown [12] that this prevents the occurrence of chemical instability (which as repeatedly emphasized is a *far* from equilibrium phenomenon).

If we now add to (10.1) the step



where  $D_4$  is some other form of the enzyme  $D_1$ , reaction (2) goes out of equilibrium and chemical *instability may occur*. However we have not yet investigated what the state of the system beyond the chemical instability is.

Anyway we see that the idea of chemical instabilities is certainly compatible with the types of chemical reactions presently investigated in biochemical processes.

## 11. General discussion

It is certainly tempting to define living systems as open systems presenting a dissipative structure due to chemical instabilities. This definition is clearly incomplete as much more precise conditions on the type of chemical reactions involved would be necessary to explain essential features of life such as replication phenomena.

Incomplete as it is, this definition has two advantages:

- 1) it may lead to experimental investigations. Indeed no chemical instability has to our knowledge been observed *experimentally* till now;
- 2) it puts together various ideas and point of views which may be found in the literature and which at first seem contradictory. Life no longer appears as an island of resistance against the second law of thermodynamics; as the work of some Maxwell demons, but on the contrary as following the laws of physics appropriate to specific kinetic laws and to far from equilibrium conditions. These specific kinetic laws permit the flow of energy and matter to build and maintain functional and structural order.

Some authors have insisted that life follows the second law of thermodynamics [21], others have insisted that the laws of biology have a somewhat special status. Elsasser has coined the term biotonic for a causal relationship which involves an increase of "information".

Both views find a justification in our approach: indeed the entropy production remains positive both before and after the instability (9.4) but the relation between kinetics and thermodynamics changes radically as discussed in § 9.

In this paper we used a physico-chemical language. We spoke about catalytic reactions. Others may prefer to speak about negative feedback, auto-regulation and so on [23]. It will therefore be feasible to closely link our approach to information theory.

Again some authors insist on the chemical aspects of life [24, 25]. Clearly our conclusion is not in contradiction with this as precise chemical conditions are to be met to produce the chemical instabilities. Also active transport appears here as a consequence of dissipative structure. All symmetry requirements valid in the linear range of irreversible thermodynamics fail here. The maintainance of inhomogeneities ipso facto means active transport through chemical reaction rates.

But the most exciting perspective is the possibility of combining the unity of matter with a clear distinction of what is life and what not as these two states of matter would be separated by an instability corresponding to a critical affinity.

Therefore there appears at least some hope of reconciling the basic duality of our experience with the unity of the laws of nature.

I am deeply indebted to Prof. P. Glansdorff. It is in collaboration with him that the thermodynamic concepts used in this paper have been developed. I am also much indebted to Dr. G. Nicolis and M. R. Lefever for continuous help and discussion.

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#### Additional references

- More details about the scheme I in § 6 may be found in Lefever, R., *Acad. Roy. Belg., Bull. Cl. Sci.* **54** (1968) 712 and *J. Chem. Phys.*, to appear.
- The sufficient conditions for chemical instabilities are discussed in papers by Perdang, *Acad. Roy. Belg., Bull. Cl. Sci.*, (to appear) and B. Edelstein (submitted to *J. Theor. Biol.*).
- The theory of fluctuations in non-equilibrium steady states has been developed by G. Nicolis and A. Babloyantz (submitted to *J. Chem. Phys.*).

For interesting biological applications of the ideas, see B. Lavenda and G. Nicolis (submitted to *J.A.C.S.*) and B. Lavenda, *Acad. Roy. Belg., Bull. Cl. Sci.*, (to appear).



## DISCUSSIONS

E. G. D. COHEN: Dr. Fröhlich, in the preprint of your paper as well as in your lecture quantum mechanical concepts as long range order in super-conductors and superfluids seem to play an essential role.

However, as far as I can make out, the example you gave does not directly involve any quantum mechanical concepts at all and is entirely classical. This raises the question, whether classical rather than quantum mechanical analogies may not be useful for understanding some aspects of f.i. cooperative phenomena of cells.

M. KATCHALSKY: The case discussed by Dr. Fröhlich has a classical counterpart in the organization of small molecules in the formation of micelles, well known from colloid chemical studies. Recent investigations mainly by Luzatti have shown that lipid molecules in aqueous solution form two types of micelles (a) bilayer sheets or (b) infinite cylindrical structures. My colleague, Dr. Adrian Parsegian has shown that the stability of these micelles could be fully explained by the electrostatic double layer interaction (of the type evaluated by us for poly-electrolytes) and by short range forces determining the conventional surface tension. This field of colloid chemistry seems therefore to be adequately covered by a classical treatment.

I would like to ask Dr. Fröhlich whether he sees in the quantum mechanical wave treatment the possibility of predicting new phenomena which are not understood by the classical approach. Since the biologists are very interested in long range interactions, which govern the behaviour of lipoprotein membranes, such a prediction would be very valuable.

H. FRÖHLICH: Mon impression est que c'est là un cas classique, dont j'ai parlé moi-même. Bien entendu, les forces que vous pouvez avoir dans telle ou telle succession peuvent être traitées de la manière que je vous ai dite. Plus loin, vous avez de toute façon la mécanique quantique, dans ce domaine.

Je dois dire que j'adhère à tout ce dont vous avez parlé. Cependant, il y a certaines limites statistiques. J'ai moi-même puisé dans un des principes de M. Prigogine, à savoir qu'à travers le système (nous pourrions en reparler), il se pourrait qu'il y ait, en effet, . . .

I. SEGAL: What is the biological counterpart to the quanta which should be associated with this model in accordance with the general principles of quantum mechanics? Perhaps it is due to my ignorance of biology, but I don't understand what the biological counterpart of the photon is proposed to be.

H. FRÖHLICH: I am not introducing single photons in connection with the example I gave. What I proposed here is, instead of taking phonons, to take what sometimes is called "plasmons". But the individual quantum would be negligible if there is a similarity with lasers or with coherent sound waves; the longitudinal plasma would oscillate essentially as classically.

E. G. D. COHEN: Do you believe that it is *always* useful to consider biological systems from a quantum mechanical point of view? Or would you be prepared to say that in certain cases—where f.i. a large number of entities is involved—it might be more simple and more adequate to forget the quantum mechanical basis and use a classical model or analogy for the understanding of biological phenomena?

H. FRÖHLICH: La situation est compliquée. Depuis des années, les gens qui s'occupent des "lasers" ont affaire à la mécanique quantique, que d'autres ont pu laisser de côté. Aussi, vous pouvez oublier ce côté et vous pouvez fort bien étudier les choses de manière classique. Mais on ne peut pas toujours le faire! De toute façon, tout cela n'intéresse pas les biologistes.

L. ROSENFELD: There is a simple criterium to distinguish classical from quantal effects: if in the expression obtained for an observable quantity Planck's constant appears explicitly, one may say that it represents a quantal effect. If, however, the observable quantity does not depend on Planck's constant, it means that one is in the classical domain.

H. FRÖHLICH: I am afraid we are getting off the biologists. But there is a very interesting example I shall give you privately where the  $h$  does not appear.

H. HAKEN: Let us consider an arrangement of atoms which are excited and are starting to emit spontaneously light. In general these spontaneously emitted light waves are not in phase (e.g. they are incoherent). This emission process is a purely quantum mechanical effect. It may happen that a simple photon hits another excited atom and causes the atom to recombine emitting a second photon by the process of stimulated emission. This process is still a quantum mechanical effect. It may be continued several times so that a macroscopic number of photons is generated. Now the question is: is this phenomenon still a quantum mechanical one or does it already belong to classical physics. In the mathematical treatment one starts with the description of the light by a photon creation operator which contains all the quantum mechanical fluctuations. But if the photon number increases one indeed ends up under certain conditions with a classical lightfield amplitude. Thus one starts with the random process of spontaneous emission and ends up with a new structure, a new organization on a microscopic scale.

H. L. LONGUET-HIGGINS: I should like to raise a point which Dr. Fröhlich and I discussed during the coffee break. In the course of his talk Dr. Fröhlich suggested that electrical resonance between cells might trigger cell division. But a cell can divide when there are no other cells around, and this process is a very complicated business in which the individual parts form a highly organized whole, rather like a cocktail party at which the guests divide themselves into two groups. The relation between this process and the double layer oscillations proposed by Dr. Fröhlich is quite unclear to me. Perhaps Dr. Fröhlich would care to comment on this point?

H. FRÖHLICH: First point. I did say it stimulates, not causes. But it is not a stimulation through an oscillation which would be much too fast for something mechanical to follow. It is stressed through deformation.

Biological systems are highly organised. There should be resonances with certain molecular oscillations in some way or other.

H. C. LONGUET-HIGGINS: The other point which I wanted to discuss is the question of the resonance of the individual molecules inside a cell. There are various degrees of freedom that one might consider – translational, rotational, torsional and electronic. In metals there are electronic oscillations which are quite distinct from individual particle motions, but it does seem that most molecules of biological importance, particularly the colourless ones which make up the bulk of most cells, are electronically quite normal. It does seem rather far-fetched to suggest that such molecules have plasma oscillations in the microwave region, or that such oscillations could arise spontaneously, in view of the viscous damping due to the neighbouring molecules. Such questions have been the subject of heated discussion among physical chemists, in particular whether proteins and nucleic acids have electronic excitations which are important biologically. My own view is that the case is a very dubious one at the moment.

G. CARERI: I believe one can extend the Fröhlich model to the intracellular long range interactions, which perhaps are responsible for the unity of the cell as a whole. As a matter of fact inside the cell one can identify in the proteins the polarizable entities which can interact in the collective longitudinal mode according to the Fröhlich model. Most likely the oscillators can be found in the hydrogen bonded NH...O chains which should exhibit some longitudinal modes in the very far infrared (say 10 to 50  $\text{cm}^{-1}$ ). A detailed theoretical calculation is lacking, but one has good reason to expect these modes in that range, following the same arguments which usually explain hypochromism in a chain of coupled oscillators, because the stretching frequency of the single hydrogen bond is at about 200  $\text{cm}^{-1}$ . So far the polarizability of the biological matter has not been studied in this region of the electromagnetic spectrum,

because of the obvious difficulties; experiments of this kind are now in progress in our laboratory. Therefore as yet there are not experimental data available to prove this possibility for intracellular interactions, but let me emphasize that it is precisely in this range of e.m. radiation that one must look for collective effects. This is because at lower frequencies (namely in the microwaves) the continuous Debye relaxation of free water molecules displays its dissipative absorption, while at higher frequencies there are many absorption peaks due to the molecular modes which would trap the collective modes. It is gratifying that the Fröhlich estimated membrane frequency also falls in this region.

The need for collective intracellular effects has been already suggested on a different molecular basis by Elsasser (J. Theor. Biology 1962) to create in the organism a high degree of physical unpredictability. The way they are introduced here has the advantage of a clear similarity in the pattern or the collective behaviour both inside the living cell and among the cells in the organism, displaying just that hierarchy character between the ordered units and subunits as expected in biology (see for instance, P. Weiss, Rev. Mod. Phys. 1959). However, it must be remembered that up to today it has not been proved that there are such long range effects between the cell subunits.

L. ROSENFELD: I notice that we are deviating from specific questions to questions of principle. So I should like to suggest that, unless somebody is really very impatient to ask Dr. Fröhlich a specific question, we now postpone the discussion about the Fröhlich paper and pass to the preliminary discussion of Dr. Prigogine's paper.

K. MENDELSSOHN: Dr. Fröhlich has mentioned the superfluids in connection with more general questions of the solid state. Having regard to the high degree of orderliness which is a basic feature of living matter, the superfluids present an order pattern which is rather unusual. These phenomena, superfluidity in liquid helium and superconductivity, occur at very low absolute temperatures. This in itself indicates that the entropy is low, i.e. the degree of order high. Moreover, measurement of the entropy reveals that at the onset of these states a further sharp decrease of entropy takes place.

The usual feature which we associate with the cooling of matter is the phenomenon of condensation in which the drop in entropy is expressed by the fact that the atoms take up an orderly pattern in a crystal lattice. This is an order in respect of *position* and, indeed, ordering in position space is the only form of an orderly arrangement which we can easily comprehend.

However, no such thing happens at the onset of superfluidity; helium remains a liquid and the electrons in a superconductive metal remain free. Orderliness, which we know exists, must be manifest in another way than by a pattern in position. The obvious place to look for it, is not the space of positions but that

of momenta. Indeed, the unusual properties which we observe in the superfluids are all connected with the phenomena of motion.

We know not nearly enough about the superfluids to be able to treat the onset in the same way as the formation of a crystal. However, most people will agree that in the superfluids we witness a new type of aggregation of matter in which some sort of condensation according to the momentum co-ordinates seems to take place. As I just said, the relevant phenomena are given by a frictionless form of motion and this velocity structure is evidently spread over the whole volume of the superfluid.

We thus know structures which are ordered in position, the crystals, and structures which are ordered in momenta, the superfluids. Inevitably the question arises whether we can conceive of structures which show *both* types of order simultaneously. From our knowledge of the solid state and of the superfluids we can hazard some conclusions as to the properties of such structures. First of all their statistical order must be very high, that is they must be statistically extremely improbable. Secondly they must have form and shape like a solid. Thirdly, they must have the property of superfluids that is, what happens to one part of the structure will affect the whole. To give an example: if you have a metal ring with a supercurrent flowing through it, local quenching of superconductivity at any part of the ring will destroy the current everywhere in the ring.

It now appears, when we summarize all these features, that our hypothetical structures which are ordered in position *and* momentum possess features which we associate with the structures of living matter.

H. FRÖHLICH: I agree. What there is to be said I think is equivalent to Dr. Haken's remarks. The remark I wanted to make on Prigogine's paper concerns the use of the entropy concept. Now what do we know about life? One thing that it is statistically improbable, but the structures of life are certainly an improbable structure. But this does not mean that the entropy concept helps us entirely. The entropy concept may not reflect the correct improbability which we need.

Let's see. Consider a mouse or a flea or a protein molecule. Then it is made of a certain number of atoms. Now you can actually arrange the same number of atoms of the mouse and an equally improbable structure and an infinite number of equally improbable structures only the mouse will not live. So you see somehow the entropy concept is insufficient. The concept which I needed I think is one of a selective organization referring to few degrees of freedom only, and hence not relevant for entropy.

I. PRIGOGINE: Je crois que vous me demandez trop. La notion de structure dissipative n'est sûrement pas suffisante à elle seule pour expliquer la vie. D'autres éléments fondamentaux doivent intervenir pour expliquer par exemple la duplication. Le point important que je voulais souligner c'est que la physico-chimie

permet actuellement de comprendre l'apparition de situations hautement improbables du point de vue entropie.

Quant à la superfluidité qui a été évoquée à plusieurs reprises, je crois que l'analogie avec les phénomènes vitaux est fort trompeuse. La caractéristique des phénomènes à basse température telle que superfluidité ou superconductivité est précisément l'absence ou la faible importance de phénomènes de dissipation.

Au contraire les structures de la biologie moléculaire exigent un flux d'énergie et de matières continues. Ce sont des structures de non-équilibre et je ne crois dès lors pas que l'analogie avec les phénomènes à basse température nous apprendra grand chose.

H. FRÖHLICH: I will answer to Dr. Mendelssohn that this is the crucial point. The point which I made is that the deviation from thermal equilibrium refers to a very few degrees of freedom only. But it's the essential point, nevertheless, at least in my thinking.

Secondly, there is no suggestion of saying that you have in our system the same type of stabilisation as you have in superconductors and in superfluids. Quite on the contrary, as I mentioned explicitly, the stabilisation there is either energetical or quantum mechanical. Here something else is required which requires a supply of energy and secondly it requires non-linear effects.

Nevertheless the deeper structure of this correlation has very great similarity in both cases. Dr. Haken has also mentioned in detail the case of lasers which also show a similar type of correlation.

J. POLONSKY: J'aimerais apporter ici quelques remarques d'un ingénieur en électronique sur le "many body problem" évoqué par M. Fröhlich, tel qu'il se pose pour des systèmes hautement organisés, artificiels ou biologiques.

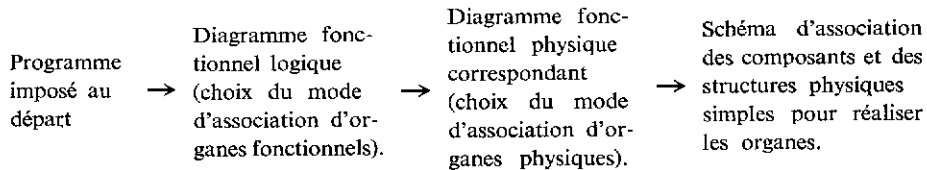
Il est connu que tout système organisé doit être alimenté en régime dynamique par une source d'énergie externe capable de compenser l'accroissement d'entropie totale produit dans le système au cours de son fonctionnement. La thermodynamique des systèmes non en équilibre, dont nous a entretenu M. Prigogine, permet d'étudier les échanges d'énergie ainsi que les contraintes thermodynamiques extensives et intensives qui interviennent au cours de ces échanges.

Il est connu, par ailleurs, que dans un système hautement organisé, le réseau des contraintes à caractère informationnel prend le pas sur le réseau d'énergie et sur les contraintes purement thermodynamiques. Le rôle prioritaire joué par les contraintes informationnelles provient du fait que celles-ci, avec une dépense d'énergie minime, exercent des asservissements hiérarchisés dans le système et déterminent le mode fonctionnel du système organisé. La structure du réseau informationnel dans un dispositif cybernétique (comme par exemple le pilotage automatique d'un avion ou d'un satellite) ne peut pas être étudiée par la thermodynamique. Il est un fait qu'il nous manque une véritable science des systèmes

organisés. En attendant que celle-ci voie le jour, il me semble utile, pour l'objet de notre discussion, d'exposer brièvement la méthode d'approche utilisée par l'ingénieur dans ce domaine, d'examiner dans quelle mesure celle-ci peut être étendue à la biologie et quel pourrait être le rôle des concepts quantiques dans cette approche.

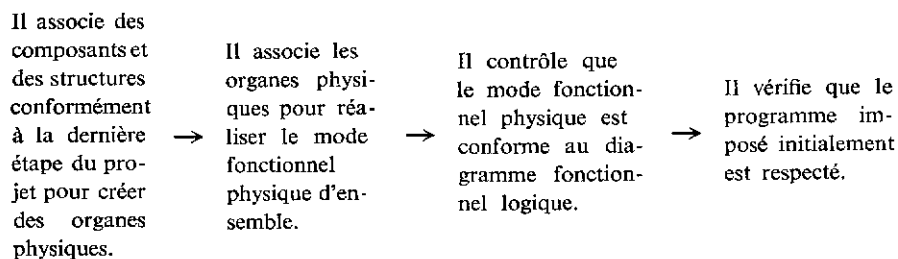
L'ingénieur procède en deux étapes:

1. Au cours du projet d'un dispositif cybernétique artificiel, il opère dans l'ordre suivant:



Dans cette étude, les deux premières étapes sont d'ordre logique, tandis que les deux dernières se situent sur un plan physique.

2. Pendant la phase de réalisation de l'appareil, l'ingénieur opère en sens inverse.



Ce dernier diagramme pourrait convenir à l'étude de la formation d'un système biologique en substituant, dans les associations, la finalité par des lois physiques. Néanmoins, en électronique, le modèle fonctionnel précède le choix de la structure physique correspondante tandis qu'en biologie, la structure physique précède et crée ipso facto la fonction biologique. La philosophie qui se dégage de cette méthode d'approche pourrait se résumer comme suit:

Toute étape de formation ou de complexification d'un système organisé est caractérisée, sur le plan analytique, par l'élimination sélective des degrés de liberté ou l'introduction dans le système global d'un nombre croissant de corrélations sélectives sous forme de contraintes des probabilités régies par des lois stochastiques. La distribution spécifique des contraintes (et par voie de conséquence le mode fonctionnel du système) est réalisée grâce au schéma particulier

d'association des composants et des sous-ensembles. Ceci reste vrai en électronique comme en biologie.

Un système organisé, placé dans une telle optique, permet, me semble-t-il, de mieux apprécier le rôle qui pourrait être dévolu aux concepts quantiques en biologie. En effet, dans la mesure où l'on doit tenir compte des lois quantiques dans un système, celles-ci introduisent, d'une façon naturelle, une distribution fine des contraintes des probabilités, chose inconnue en physique classique. La discontinuité d'états et des transitions, les règles de sélection et d'exclusion, imposées par les concepts quantiques, sont équivalentes, du point de vue de la théorie de Shannon, à des matrices des probabilités d'états et des transitions d'états dans un processus stochastique. Comme il est connu, par ailleurs, que les contraintes quantiques sont d'autant plus sévères que les dimensions du système sont plus réduites et que l'échelle d'organisation biologique est à base moléculaire, il paraît logique que les contraintes quantiques jouent un rôle très important en cybernétique biologique. Le langage de l'information et du codage utilisé dans les communications entre molécules et macromolécules biologiques pourrait ainsi être exprimé en termes quantiques. De même l'ensemble des corrélations d'origine quantique qui régissent les interactions entre structures moléculaires jouent, sur le plan fonctionnel, le rôle de redondance prise au sens de la théorie de l'information, c'est-à-dire d'une information fixe à priori.

J'espère pouvoir, au cours de la discussion de cet après-midi, préciser davantage le rôle cybernétique des contraintes quantiques en biologie moléculaire en me référant, en particulier, au concept de cellules dans l'extension en phase pris au sens de la mécanique statistique.

H. C. LONGUET-HIGGINS: I think I now understand Dr. Fröhlich's hypothesis. First, if I am not mistaken, one can state it in classical terms. Secondly, he postulates the excitability of certain oscillations, and it is the oscillatory character that he is stressing. The situation seems mathematically similar to the blowing of a flute, where one has a non-linear coupling between the jet of air and what happens inside the flute; by blowing one excites the principal vibration of the air in the flute. The oscillations which Dr. Fröhlich is particularly thinking about are electrical oscillations associated with the double membrane layer. The hypothesis is really that the non-linear coupling between the metabolic dissipation and these particular modes is sufficient to keep them in a state quite far from equilibrium; this is the essence of the hypothesis. The quantum-mechanical aspect of the matter does not seriously disturb the description which I have given — or does it? I ask you this question to make sure whether I have fully understood you or not.

P. MAZUR: I assume that within the framework of your theory you obtain a formal expression for the length which characterizes the structure that arises as



a consequence of the stability conditions within a chemical system of the type you discuss. Do you have any estimate of the order of magnitude of this length. I believe this would tell us something about the implications of such a theory for biological systems.

J. DUCHESNE: Si j'ai bien compris M. Prigogine, sa théorie suppose que le métabolisme est la vie elle-même. Or, on sait bien qu'à très basse température, au voisinage du zéro absolu, et dans un état de dessèchement profond, les cellules vivantes ne sont pas détruites, bien que leur métabolisme soit supprimé. Je crois, par conséquent, que, pour saisir complètement les phénomènes vitaux, il faudrait notamment pouvoir identifier les structures limites à partir desquelles la vie ne peut se rétablir. Ceci permettrait sans doute d'élargir notre conception du phénomène vital et en même temps d'englober cet aspect des choses dans les admirables inférences de Prigogine.

I. PRIGOGINE: Pour répondre à la question de M. Duchesne, 'survivre n'est pas vivre'. Le problème que j'ai discuté est la création de structures, non le maintien de ces structures, ce qui est un tout autre problème.

W. M. ELSASSER: I would like to make a comment on the memoir of Dr. Prigogine. He has two types of systems, stable and unstable. The latter have positive exponentials so that the instability is more or less violent. I would like to point out that there exists a third category of instability which is much more general and which for some reasons biochemists have not considered. I have searched for many years but I have not been able to handle the mathematical tools.

That is the case of systems which have stereo asymmetry without an inversion appearing. These systems have the ability of going off slowly from equilibrium. As I happened to be a geophysicist for many years, I am very familiar with these systems because all of the hydrodynamics of geophysics is dominated by asymmetrical forces (the Corioly forces). I believe it would be worthwhile to look into these systems first.

Pasteur has said something very profound when he said that the stereo-asymmetry of molecules is a fundamental property of living matter. It leads immediately to problems of probability which are asymmetrical and this will lead to deviation from a stable state of equilibrium. I believe that you now have the tools to handle this. In this beautiful presentation you have given us the mathematical tools so that perhaps one can now begin to study this third intermediate category. I would not be surprised that it is perhaps as important for biology as the kind of instability which you have considered.

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