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Biological Fluid Dynamics, Non-linear Partial Differential Equations

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Glossary

Swimming The ability to advance in a fluid in the absence of external propulsive forces by performing cyclic shape changes.

Navier–Stokes equations A system of partial differential equations describing the motion of a simple viscous incompressible fluid (a Newtonian fluid)

$$\rho \left(\frac{\partial v}{\partial t} + (v \cdot \nabla) v \right) = -\nabla p + \eta \Delta v$$

$$\operatorname{div} v = 0$$

where v and p are the velocity and the pressure in the fluid, ρ is the fluid density, and η its viscosity. For simplicity external forces, such as gravity, have been dropped from the right hand side of the first equation, which expresses the balance between forces and rate of change of linear momentum. The second equation constrains the flow to be volume preserving, in view of incompressibility.

Reynolds number A dimensionless number arising naturally when writing Navier–Stokes equations in non-dimensional form. This is done by rescaling position and velocity with $x^* = x/L$ and $v^* = v/V$, where L and V are characteristic length scale and velocity associated with the flow. Reynolds number (Re) is defined by

$$\text{Re} = \frac{VL\rho}{\eta} = \frac{VL}{\nu}$$

where $\nu = \eta/\rho$ is the kinematic viscosity of the fluid, and it quantifies the relative importance of inertial versus viscous effects in the flow.

Steady Stokes equations A system of partial differential equations arising as a formal limit of Navier–Stokes equations when $\text{Re} \rightarrow 0$ and the rate of change of the data driving the flow (in the case of interest here, the velocity of the points on the outer surface of a swimmer) is slow

$$\begin{aligned} -\eta\Delta v + \nabla p &= 0 \\ \text{div } v &= 0. \end{aligned}$$

Flows governed by Stokes equations are also called creeping flows.

Microscopic swimmers Swimmers of size $L = 1\mu\text{m}$ moving in water ($\nu \sim 1\text{mm}^2/\text{s}$ at room temperature) at one body length per second give rise to $\text{Re} \sim 10^{-6}$. By contrast, a 1 m swimmer moving in water at $V = 1\text{m/s}$ gives rise to a Re of the order 10^6 .

Biological swimmers Bacteria or unicellular organisms are microscopic swimmers; hence their swimming strategies cannot rely on inertia. The devices used for swimming include rotating helical flagella, flexible tails traversed by flexural waves, and flexible cilia covering the outer surface of large cells, executing oar-like rowing motion, and beating in coordination. Self propulsion is achieved by cyclic shape changes described by time periodic functions (*swimming strokes*). A notable exception is given by the rotating flagella of bacteria, which rely on a submicron-size rotary motor capable of turning the axis of an helix without alternating between clockwise and anticlockwise directions.

Swimming microrobots Prototypes of artificial microswimmers have already been realized, and it is hoped that they can evolve into working tools in biomedicine. They should consist of minimally invasive, small-scale self-propelled devices engineered for drug delivery, diagnostic, or therapeutic purposes.

Definition of the Subject

Swimming, i. e., being able to advance in a fluid in the absence of external propulsive forces by performing cyclic shape changes, is particularly demanding at low Reynolds numbers (Re). This is the regime of interest for micro-organisms and micro-robots or nano-robots, where hydrodynamics is governed by Stokes equations. Thus, besides the rich mathematics it generates, low Re propulsion is of great interest in biology (How do microorganism swim? Are their strokes optimal and, if so, in which sense? Have these optimal swimming strategies been selected by evolutionary pressure?) and biomedicine (can small-scale self-propelled devices be engineered for drug delivery, diagnostic, or therapeutic purposes?).

For a microscopic swimmer, moving and changing shape at realistically low speeds, the effects of inertia are negligible. This is true for both the inertia of the fluid and the inertia of the swimmer. As pointed out by Taylor [10], this implies that the swimming strategies employed by bacteria and unicellular organism must be radically different from those adopted by macroscopic swimmers such as fish or humans. As a consequence, the design of artificial microswimmers can draw little inspiration from intuition based on our own daily experience.

Taylor's observation has deep implications. Based on a profound understanding of low Re hydrodynamics, and on a plausibility argument on which actuation mechanisms are physically realizable at small length scales, Berg postulated the existence of a sub-micron scale rotary motor propelling bacteria [5]. This was later confirmed by experiment.

Introduction

In his seminal paper *Life at low Reynolds numbers* [8], Purcell uses a very effective example to illustrate the subtleties involved in microswimming, as compared to the swimming strategies observable in our mundane experience. He argues that at low Re, any organism trying to swim adopting the reciprocal stroke of a scallop, which moves by opening and closing its valves, is condemned to the frustrating experience of not having advanced at all at the end of one cycle.

This observation, which became known as the *scallop theorem*, started a stream of research aiming at finding the simplest mechanism by which cyclic shape changes may lead to effective self propulsion at small length scales. Purcell's proposal was made of a chain of three rigid links moving in a plane; two adjacent links swivel around joints and are free to change the angle between them. Thus, shape is described by two scalar parameters (the angles between adjacent links), and one can show that, by changing them independently, it is possible to swim.

It turns out that the mechanics of swimming of Purcell's three-link creature are quite subtle, and a detailed understanding has started to emerge only recently [4,9]. In particular, the direction of the average motion of the center of mass depends on the geometry of both the swimmer and of the stroke, and it is hard to predict by simple inspection of the shape of the swimmer and of the sequence of movements composing the swimming stroke. A radical simplification is obtained by looking at axisymmetric swimmers which, when advancing, will do so by moving along the axis of symmetry. Two such examples are the three-sphere-swimmer in [7], and the push-me-pull-you in [3]. In fact, in the axisymmetric case, a simple and complete mathematical picture of low Re swimming is now available, see [1,2].

The Mathematics of Swimming

This article focuses, for simplicity, on swimmers having an axisymmetric shape Ω and swimming along the axis of symmetry, with unit vector $\vec{l}$. The configuration, or state s of the system is described by $N + 1$ scalar parameters: $s = \{x^{(1)}, \dots, x^{(N+1)}\}$. Alternatively, s can be specified by a position c (the coordinate of the center of mass along the symmetry axis) and by N shape parameters $\xi = \{\xi^{(1)}, \dots, \xi^{(N)}\}$. Since this change of coordinates is invertible, the generalized velocities $u^{(i)} := \dot{x}^{(i)}$ can be represented as linear functions of the time derivatives of position and shape:

$$(u^{(1)}, \dots, u^{(N+1)})^t = A(\xi^{(1)}, \dots, \xi^{(N)})(\dot{\xi}^{(1)}, \dots, \dot{\xi}^{(N)}, \dot{c})^t \quad (1)$$

where the entries of the $N + 1 \times N + 1$ matrix A are independent of c by translational invariance.

Swimming describes the ability to change position in the absence of external propulsive forces by executing a cyclic shape change. Since inertia is being neglected, the total drag force exerted by the fluid on the swimmer must also vanish. Thus, since all the components of the total force in directions perpendicular to $\vec{l}$ vanish by symmetry,

self-propulsion is expressed by

$$0 = \int_{\partial\Omega} \sigma n \cdot \vec{l} \quad (2)$$

where σ is the stress in the fluid surrounding Ω , and n is the outward unit normal to $\partial\Omega$. The stress $\sigma = \eta(\nabla v + (\nabla v)^t) - p\text{Id}$ is obtained by solving Stokes equation outside Ω with prescribed boundary data $v = \bar{v}$ on $\partial\Omega$. In turn, $\bar{v}$ is the velocity of the points on the boundary $\partial\Omega$ of the swimmer, which moves according to (1).

By linearity of Stokes equations, (2) can be written as

$$\begin{aligned} 0 &= \sum_{i=1}^{N+1} \varphi^{(i)}(\xi^{(1)}, \dots, \xi^{(N)}) u^{(i)} \\ &= A^t \Phi \cdot (\dot{\xi}^{(1)}, \dots, \dot{\xi}^{(N)}, \dot{c})^t \end{aligned} \quad (3)$$

where $\Phi = (\varphi^{(1)}, \dots, \varphi^{(N)})^t$, and we have used (1). Notice that the coefficients $\varphi^{(i)}$ relating drag force to velocities are independent of c because of translational invariance. The coefficient of $\dot{c}$ in (3) represents the drag force corresponding to a rigid translation along the symmetry axis at unit speed, and it never vanishes. Thus (3) can be solved for $\dot{c}$, and we obtain

$$\dot{c} = \sum_{i=1}^N V_i(\xi^{(1)}, \dots, \xi^{(N)}) \dot{\xi}^{(i)} = V(\xi) \cdot \dot{\xi}. \quad (4)$$

Equation (4) links positional changes to shape changes through shape-dependent coefficients. These coefficients encode all hydrodynamic interactions between Ω and the surrounding fluid due to shape changes with rates $\dot{\xi}^{(1)}, \dots, \dot{\xi}^{(N)}$.

A stroke is a closed path γ in the space S of admissible shapes given by $[0, T] \ni t \mapsto (\xi^{(1)}, \dots, \xi^{(N-1)})$. Swimming requires that

$$0 \neq \Delta c = \int_0^T \sum_{i=1}^N V_i \dot{\xi}^{(i)} dt \quad (5)$$

i. e., that the differential form $\sum_{i=1}^N V_i d\xi^{(i)}$ is not exact.

The Scallop Theorem Proved

Consider a swimmer whose motion is described by a parametrized curve in two dimensions ($N = 1$), so that (4) becomes

$$\dot{c}(t) = V(\xi(t)) \dot{\xi}(t), \quad t \in \mathbb{R}, \quad (6)$$

and assume that $V \in L^1(S)$ is an integrable function in the space of admissible shapes and $\xi \in W^{1,\infty}(\mathbb{R}; S)$ is a Lipschitz-continuous and T -periodic function for some $T > 0$, with values in S .

Figure 1 is a sketch representing concrete examples compatible with these hypotheses. The axisymmetric case consists of a three-dimensional cone with axis along $\vec{i}$ and opening angle $\xi \in [0, 2\pi]$ (an *axisymmetric octopus*). A non-axisymmetric example is also allowed in this discussion, consisting of two rigid parts (*valves*), always maintaining mirror symmetry with respect to a plane (containing $\vec{i}$ and perpendicular to it) while swiveling around a joint contained in the symmetry plane and perpendicular to $\vec{i}$ (a *mirror-symmetric scallop*), and swimming parallel to $\vec{i}$.

Among the systems that are *not* compatible with the assumptions above are those containing helical elements with axis of rotation $\vec{i}$, and capable of rotating around $\vec{i}$ always in the same direction (call θ the rotation angle). Indeed, a monotone function $t \mapsto \theta(t)$ is not periodic.

The celebrated “scallop theorem” [8] states that, for a system like the one depicted in Fig. 1, the net displacement of the center of mass at the end of a periodic stroke will always vanish. This is due to the linearity of Stokes equation (which leads to symmetry under time reversals), and to the low dimensionality of the system (a one-dimensional periodic stroke is necessarily reciprocal). Thus, whatever forward motion is achieved by the scallop by closing its valves, it will be exactly compensated by a backward motion upon reopening them. Since the low Re world is unaware of inertia, it will not help to close the valves quickly and reopen them slowly. A precise statement and a rigorous short proof of the scallop theorem are given below.

Theorem 1 Consider a swimmer whose motion is described by

$$\dot{c}(t) = V(\xi(t))\dot{\xi}(t), \quad t \in \mathbb{R}, \quad (7)$$

with $V \in L^1(S)$. Then for every T -periodic stroke $\xi \in W^{1,\infty}(\mathbb{R}; S)$, one has

$$\Delta c = \int_0^T \dot{c}(t) dt = 0. \quad (8)$$

Proof Define the primitive of V by

$$\Psi(s) = \int_0^s V(\sigma) d\sigma \quad (9)$$

so that $\Psi'(\xi) = V(\xi)$. Then, using (7),

$$\begin{aligned} \Delta c &= \int_0^T V(\xi(t))\dot{\xi}(t) dt \\ &= \int_0^T \frac{d}{dt} \Psi(\xi(t)) dt \\ &= \Psi(\xi(T)) - \Psi(\xi(0)) = 0 \end{aligned}$$

by the T -periodicity of $t \mapsto \xi(t)$.

Optimal Swimming

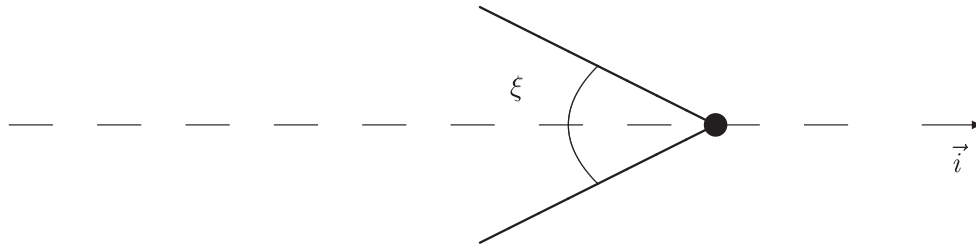
A classical notion of swimming efficiency is due to Lighthill [6]. It is defined as the inverse of the ratio between the average power expended by the swimmer during a stroke starting and ending at the shape $\xi_0 = (\xi_0^{(1)}, \dots, \xi_0^{(N)})$ and the power that an external force would spend to translate the system rigidly at the same average speed $\bar{c} = \Delta c/T$:

$$\text{Eff}^{-1} = \frac{\frac{1}{T} \int_0^T \int_{\partial\Omega} \sigma n \cdot v}{6\pi\eta L \bar{c}^2} = \frac{\int_0^1 \int_{\partial\Omega} \sigma n \cdot v}{6\pi\eta L (\Delta c)^2} \quad (10)$$

where η is the viscosity of the fluid, $L = L(\xi_0)$ is the effective radius of the swimmer, and time has been rescaled to a unit interval to obtain the second identity. The expression in the denominator in (10) comes from a generalized version of Stokes formula giving the drag on a sphere of radius L moving at velocity $\bar{c}$ as $6\pi\eta L \bar{c}$.

Let $DN: H^{1/2}(\partial\Omega) \rightarrow H^{-1/2}(\partial\Omega)$ be the Dirichlet to Neumann map of the outer Stokes problem, i. e., the map such that $\sigma n = DNv$, where σ is the stress in the fluid, evaluated on $\partial\Omega$, arising in response to the prescribed velocity v on $\partial\Omega$, and obtained by solving the Stokes problem outside Ω . The expended power in (10) can be written as

$$\int_{\partial\Omega} \sigma n \cdot v = \int_{\partial\Omega} DN(v) \cdot v. \quad (11)$$



Biological Fluid Dynamics, Non-linear Partial Differential Equations, Figure 1
A mirror-symmetric scallop or an axisymmetric octopus

At a point $p \in \partial\Omega$, the velocity $v(p)$ accompanying a change of state of the swimmer can be written as a linear combination of the $u^{(i)}$

$$v(p) = \sum_{i=1}^{N+1} \mathcal{V}_i(p, \xi) u^{(i)} \quad (12)$$

$$= \sum_{i=1}^N \mathcal{W}_i(p, \xi) \dot{\xi}^{(i)}. \quad (13)$$

Indeed, the functions $\mathcal{V}_i$ are independent of c by translational invariance, and (4) has been used to get (13) from the line above.

Substituting (13) in (11), the expended power becomes a quadratic form in $\dot{\xi}$

$$\int_{\partial\Omega} \sigma n \cdot v = (G(\xi) \dot{\xi}, \dot{\xi}) \quad (14)$$

where the symmetric and positive definite matrix $G(\xi)$ is given by

$$G_{ij}(\xi) = \int_{\partial\Omega} DN(\mathcal{W}_i(p, \xi)) \cdot \mathcal{W}_j(p, \xi) dp. \quad (15)$$

Strokes of maximal efficiency may be defined as those producing a given displacement Δc of the center of mass with minimal expended power. Thus, from (10), maximal efficiency is obtained by minimizing

$$\int_0^1 \int_{\partial\Omega} \sigma n \cdot v = \int_0^1 (G(\xi) \dot{\xi}, \dot{\xi}) \quad (16)$$

subject to the constraint

$$\Delta c = \int_0^1 V(\xi) \cdot \dot{\xi} \quad (17)$$

among all closed curves $\xi: [0, 1] \rightarrow S$ in the set S of admissible shapes such that $\xi(0) = \xi(1) = \xi_0$.

The Euler–Lagrange equations for this optimization problem are

$$-\frac{d}{dt}(G\dot{\xi}) + \frac{1}{2} \begin{pmatrix} \left(\frac{\partial G}{\partial \xi^{(1)}} \dot{\xi}, \dot{\xi} \right) \\ \vdots \\ \left(\frac{\partial G}{\partial \xi^{(N)}} \dot{\xi}, \dot{\xi} \right) \end{pmatrix} + \lambda \left(\nabla_{\xi} V - \nabla_{\xi}^t V \right) \dot{\xi} = 0 \quad (18)$$

where $\nabla_{\xi} V$ is the matrix $(\nabla_{\xi} V)_{ij} = \partial V_i / \partial \xi_j$, $\nabla_{\xi}^t V$ is its transpose, and λ is the Lagrange multiplier associated with the constraint (17).

Given an initial shape ξ_0 and an initial position c_0 , the solutions of (18) are in fact sub-Riemannian geodesics joining the states parametrized by (ξ_0, c_0) and $(\xi_0, c_0 + \Delta c)$ in the space of admissible states $\mathcal{X}$, see [1]. It is well known, and easy to prove using (18), that along such geodesics $(G(\gamma)\dot{\gamma}, \dot{\gamma})$ is constant. This has interesting consequences, because swimming strokes are often divided into a power phase, where $|G(\gamma)|$ is large, and a recovery phase, where $|G(\gamma)|$ is smaller. Thus, along optimal strokes, the recovery phase is executed quickly while the power phase is executed slowly.

The Three-Sphere Swimmer

For the three-sphere-swimmer of Najafi and Golestanian [7], see Fig. 2, Ω is the union of three rigid disjoint balls $B^{(i)}$ of radius a , shape is described by the distances x and y , the space of admissible shapes is $S = (2a, +\infty)^2$, and the kinematic relation (1) takes the form

$$\begin{aligned} u^{(1)} &= \dot{c} - \frac{1}{3}(2\dot{x} + \dot{y}) \\ u^{(2)} &= \dot{c} + \frac{1}{3}(\dot{x} - \dot{y}) \\ u^{(3)} &= \dot{c} + \frac{1}{3}(2\dot{y} + \dot{x}). \end{aligned} \quad (19)$$

Consider, for definiteness, a system with $a = 0.05$ mm, swimming in water. Calling $f^{(i)}$ the total propulsive force on ball $B^{(i)}$, we find that the following relation among forces and ball velocities holds

$$\begin{pmatrix} f^{(1)} \\ f^{(2)} \\ f^{(3)} \end{pmatrix} = R(x, y) \begin{pmatrix} u^{(1)} \\ u^{(2)} \\ u^{(3)} \end{pmatrix} \quad (20)$$

where the symmetric and positive definite matrix R is known as the resistance matrix. From this last equation, using also (19), the condition for self-propulsion $f^{(1)} + f^{(2)} + f^{(3)} = 0$ is equivalent to

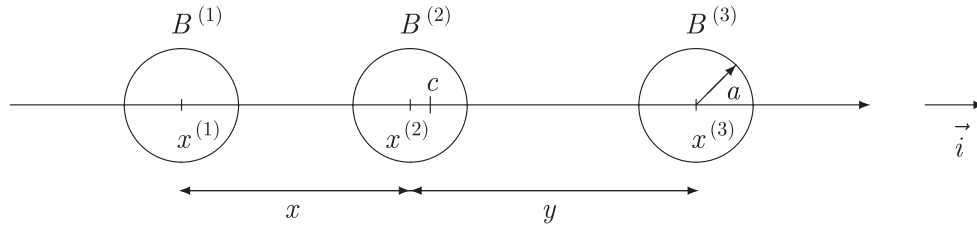
$$\dot{c} = V_x(x, y)\dot{x} + V_y(x, y)\dot{y}, \quad (21)$$

where

$$V_x(x, y) = \frac{Re_c \cdot (e_c \times e_y)}{Re_c \cdot (e_x \times e_y)} \quad (22)$$

$$V_y(x, y) = -\frac{Re_c \cdot (e_c \times e_x)}{Re_c \cdot (e_x \times e_y)}. \quad (23)$$

Moreover, $e_x = (-1, 1, 0)^t$, $e_y = (0, -1, 1)^t$, $e_c = (1/3, 1/3, 1/3)^t$.



Biological Fluid Dynamics, Non-linear Partial Differential Equations, Figure 2
Swimmer's geometry and notation

Biological Fluid Dynamics, Non-linear Partial Differential Equations, Table 1

Energy consumption (10^{-12} J) for the three strokes of Fig. 3 inducing the same displacement $\Delta c = 0.01$ mm in $T = 1$ s

Optimal stroke	Small square stroke	Large square stroke
0.229	0.278	0.914

Given a stroke $\gamma = \partial\omega$ in the space of admissible shapes, condition (5) for swimming reads

$$0 \neq \Delta c = \int_0^T (V_x \dot{x} + V_y \dot{y}) dt = \int_\omega \text{curl} V(x, y) dx dy \quad (24)$$

which is guaranteed, in particular, if $\text{curl} V$ is bounded away from zero. Strokes of maximal efficiency for a given initial shape (x_0, y_0) and given displacement Δc are obtained by solving Eq. (18). For $N = 2$, this becomes

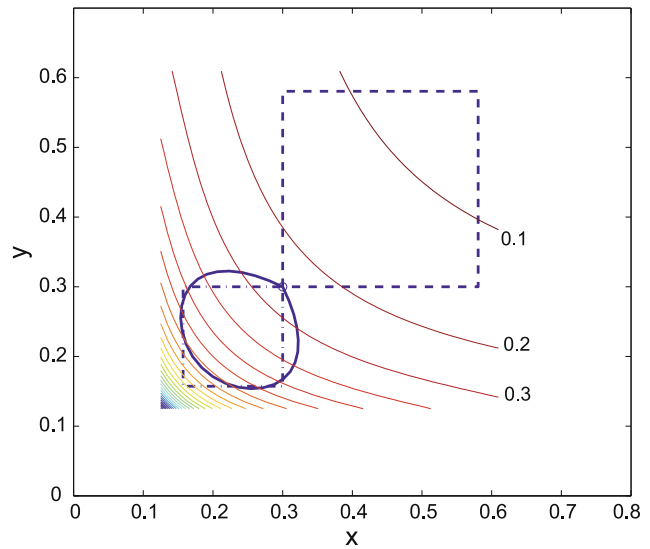
$$-\frac{d}{dt}(G\dot{\gamma}) + \frac{1}{2} \left(\begin{pmatrix} \partial_x G \dot{\gamma} \\ \partial_y G \dot{\gamma} \end{pmatrix} \right) + \lambda \text{curl} V(\gamma) \dot{\gamma}^\perp = 0 \quad (25)$$

where $\partial_x G$ and $\partial_y G$ stand for the x and y derivatives of the 2×2 matrix $G(x, y)$.

It is important to observe that, for the three-sphere swimmer, all hydrodynamic interactions are encoded in the shape dependent functions $V(x, y)$ and $G(x, y)$. These can be found by solving a two-parameter family of outer Stokes problems, where the parameters are the distances x and y between the three spheres. In [1], this has been done numerically via the finite element method: a representative example of an optimal stroke, compared to two more naive proposals, is shown in Fig. 3.

Future Directions

The techniques discussed in this article provide a head start for the mathematical modeling of microscopic swimmers, and for the quantitative optimization of their strokes. A complete theory for axisymmetric swimmers is already available, see [2], and further generalizations to



Biological Fluid Dynamics, Non-linear Partial Differential Equations, Figure 3

Optimal stroke and square strokes which induce the same displacement $\Delta c = 0.01$ mm in $T = 1$ s, and equally spaced level curves of $\text{curl} V$. The small circle locates the initial shape $\xi_0 = (0.3 \text{ mm}, 0.3 \text{ mm})$

arbitrary shapes are relatively straightforward. The combination of numerical simulations with the use of tools from sub-Riemannian geometry proposed here may prove extremely valuable for both the question of adjusting the stroke to global optimality criteria, and of optimizing the stroke of complex swimmers. Useful inspiration can come from the sizable literature on the related field dealing with control of swimmers in a perfect fluid.

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Biological Models of Molecular Network Dynamics

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Bibliography

Glossary

Deterministic continuous model A mathematical model where the variables of the model can take any real value and where the time evolution of the model is set by the initial conditions.

Stochastic discrete model A mathematical model where the variables of the model take on discrete values and where the time evolution of the model is described by a set of probability distributions.

Definition of the Subject

Understanding the operation cellular networks is probably one of the most challenging and intellectually exciting scientific fields today. With the availability of new experimental and theoretical techniques our understanding of the operation of cellular networks has made great strides in the last few decades. An important outcome of this work is the development of predictive quantitative models. Such models of cellular function will have a profound impact on our ability of manipulate living systems which will lead to new opportunities for generating energy, mitigating our impact on the biosphere and last but not least, opening up new approaches and understanding of important disease states such as cancer and aging.

Introduction

Cellular networks are some of the most complex natural systems we know. Even in a “simple” organism such as *E. coli*, there are at least four thousand genes with many thousands of interactions between molecules of many different sizes [11]. In a human cell the number of interactions is probably orders of magnitude larger. Why all this complexity? Presumably the earliest living organisms were much simpler than what we find today but competition for resources and the need to adapt in unfavorable conditions must have led to the development of sensory and decision-making capabilities above and beyond the basic requirements for life. What we see today in almost all living organisms are complex signaling and genetic networks whose complexity and subtlety is beyond most man-made technological systems [87].

Over the last sixty or so years, biochemists and molecular biologists have identified many of the components in living cells and have traced out many of the interactions that delineate cellular networks. What emerges is a picture that would be familiar to many control engineers