The Theory of Fluctuations in Gene Regulation Networks

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Population Biology

"Population biology", as this art-form is called, is one of the few uses of mathematics in biology to which all biologists are reconciled, and often with unaccustomed enthusiasm.

J. Maddox. 1998. *What Remains to be Discovered?* Simon and Schuster, New York (pg 248)

The basic principle of biological contingency:

Organisms operate by means of inhibition and conditional activation.

Together, inhibition and conditional activation create highly regulated networks and multiple phenotypes.

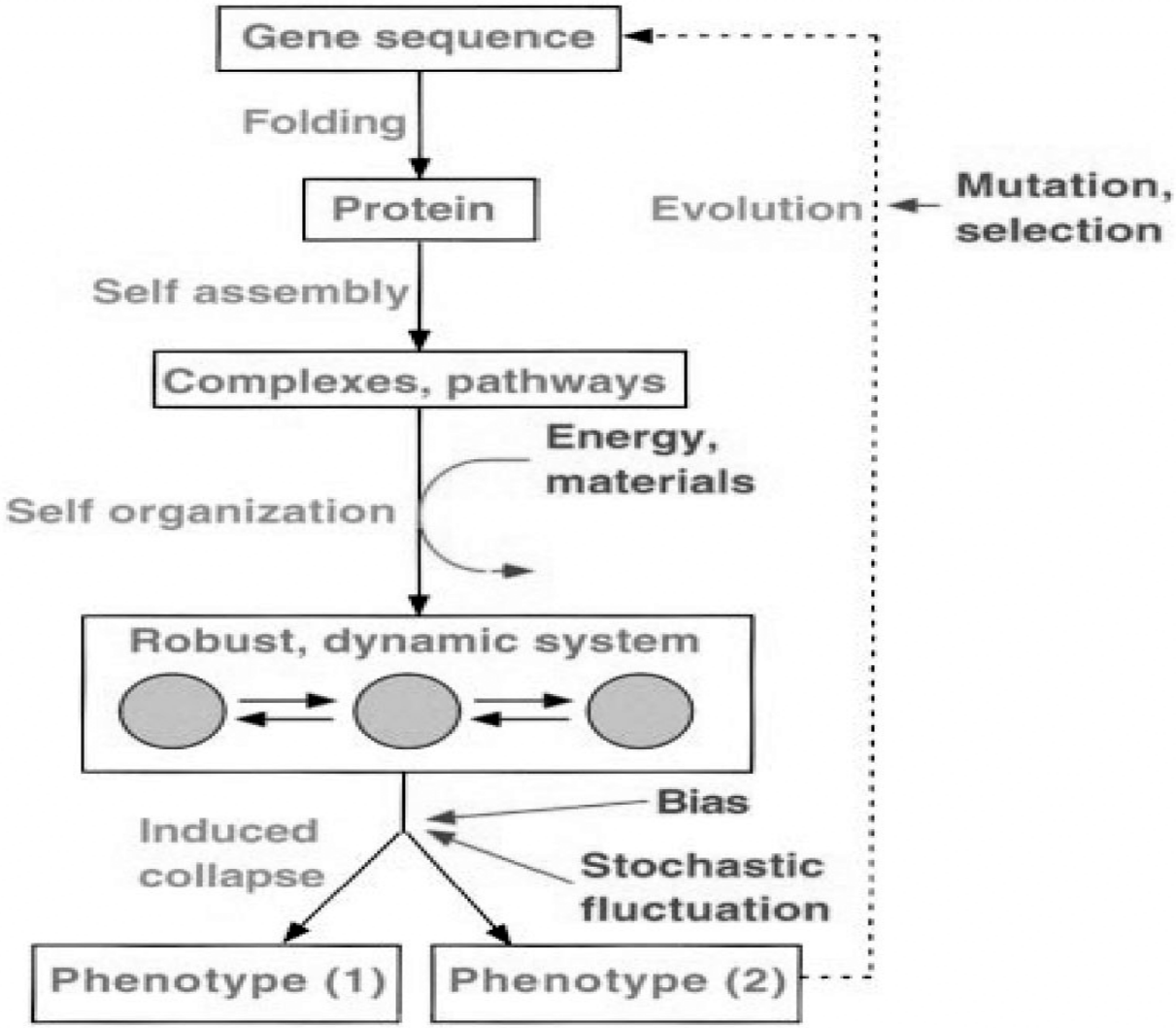
Gerhart, J. and M. Kirschner. 1997. *Cells, Embryos and Evolution.* Blackwell Science, Oxford, UK

In Autocatalytic Systems Fluctuations Are Not Noise -- They Are the Future

Kirschner, M., Gerhart, J. and T. Mitchison. 2000. Molecular "Vitalism". Cell 100:79-88

• Self organization uses two or multi-stated components to generate robust dynamic systems that can respond to external biases or *amplify stochastic fluctuations* and thus collapse into one of several potential functional states

The generation of phenotypic variation according to Kirschner et al. 2000



Fluctuations in Autocatalytic Systems

M. Delbrück. 1940. Statistical fluctuations in autocatalytic reactions. Journal of Chemical Physics 5:120-124

$$N + S \rightarrow 2N$$

$$\frac{dN}{dt} = kN$$

"While we do not feel qualified to review adequately the chemical literature on autocatalysis it should be pointed out that none of the well-known autocatalytic reactions lend themselves to the study of these fluctuations"

•The distribution of time at which a given number of particles is achieved

F.C. Frank. 1953. On spontaneous asymmetric synthesis. Biochemica Biophysica Acta 11:459

Two enantiomers, catalysts for their own production and inhibitors for the production of the alternative

$$\frac{dx}{dt} = x(1+\alpha-x-\alpha y)$$

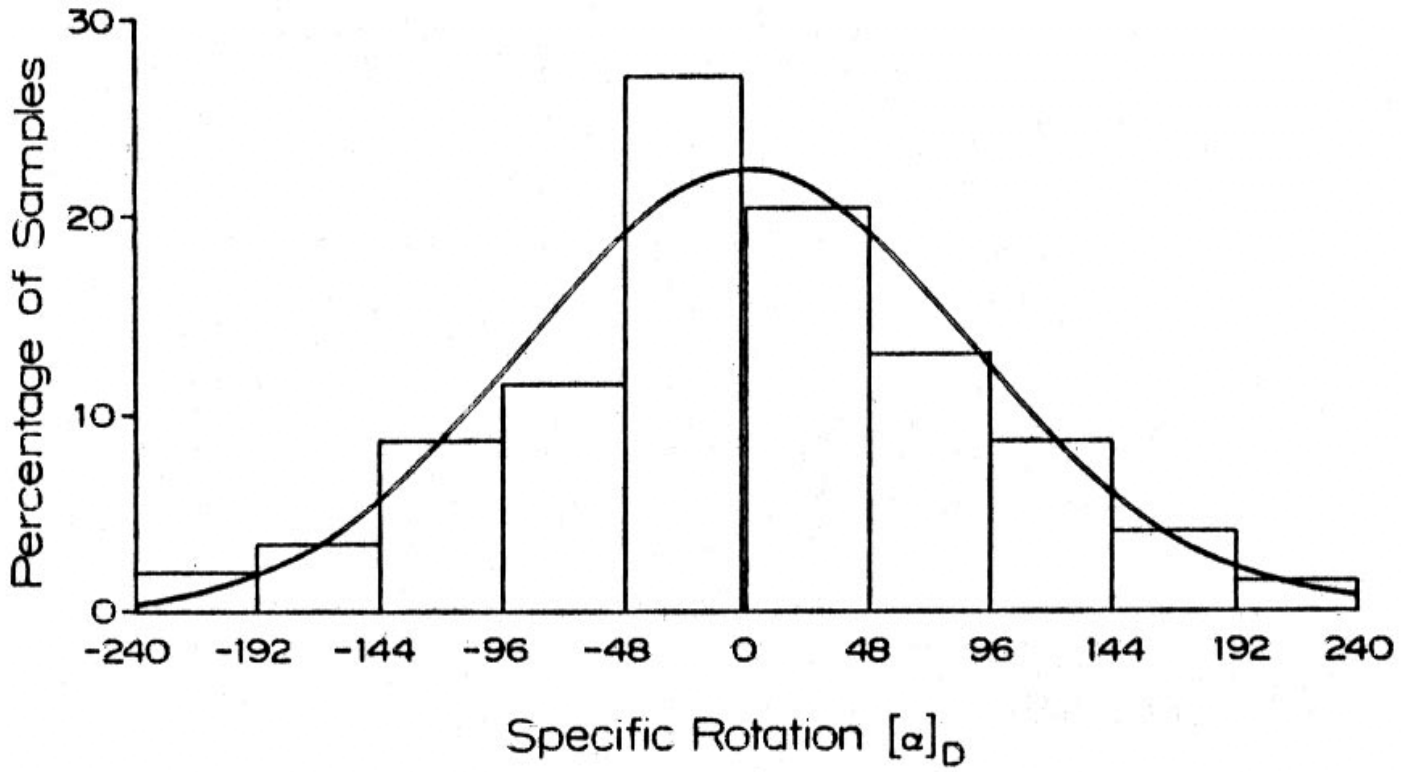
$$\frac{dy}{dt} = y(1+\alpha-y-\alpha x)$$

If $\alpha<1$, steady state is racemic. If $\alpha>1$, steady state is almost always 100% of one of the two enantiomers

R.E. Pincock et al. 1971. Probability distribution of enantimorphous forms in spontaneous generation of optically active substances. Science 174:1018-1020

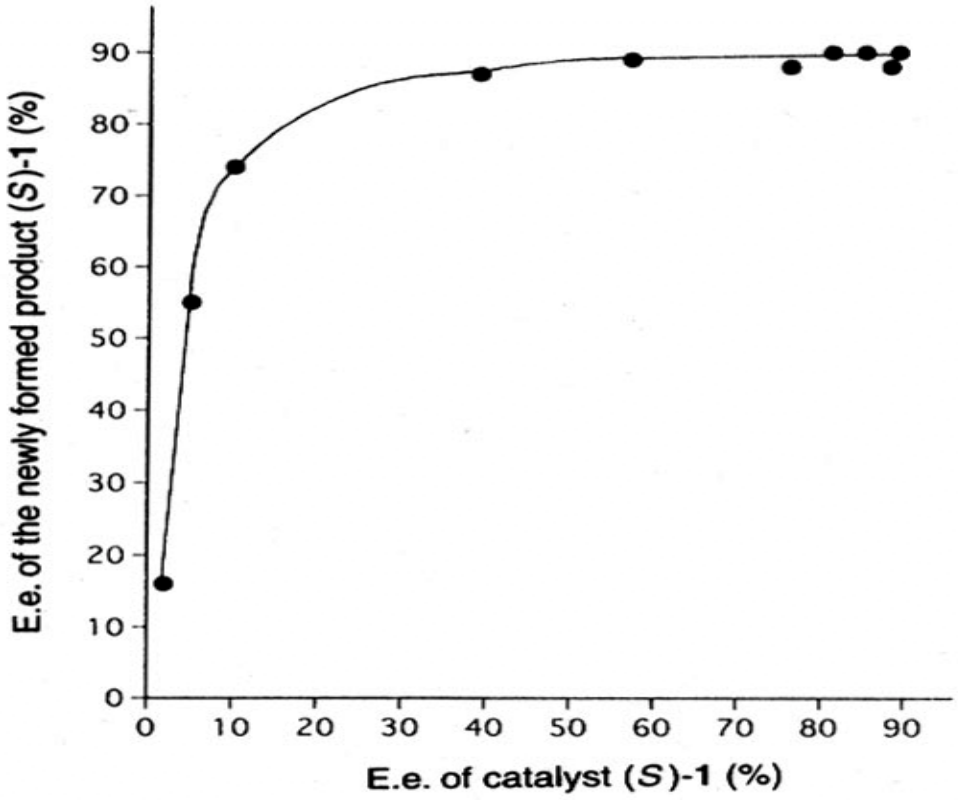
- Distribution of optical activity in crystalized binapthyl

Percentage of 200 binapthyl samples, crystalized from a melt at 170-185^{o}, giving various specific rotations and fitted Gaussian



R.E. Pincock et al. 1971. Probability distribution of enantimorphous forms in spontaneous generation of optically active substances. Science 174:1018-1020

Soa, K. et al. 1995. Asymmetric autocatalysis and amplification of enantiomeric excess of a chiral molecule. Nature 378:767-768



Nonlinear relationship between enantiomeric excess (E.e) of chiral pyrimidyl alkanol and that of the product

Soal, K. et al. 1995. Asymmetric autocatalysis and amplification of enantiomeric excess of a chiral molecule. Nature 378:767-768

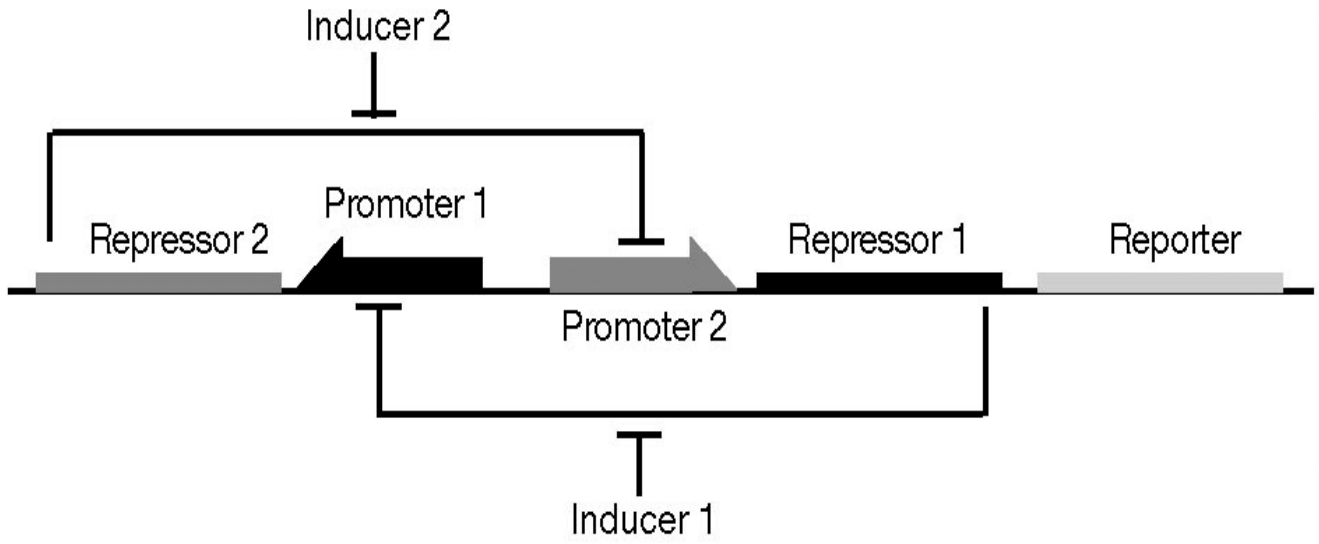
> "It seems conceivable that the reaction reported here may be an example of the scheme proposed by Frank"

Also see LG Harrison. 1993. *Kinetic Theory of Living Pattern.* Cambridge University Press.

Gardner, T.S., Cantor, C.R., and J.J. Collins.2000. Constrution of a genetic toggle switch in Escherichia coli. Nature 403:339

Gardner, T.S. 2000. Design and Construction of Synthetic Gene Regulatory Networks. Ph.D. dissertation, Boston University

Fundamental toggle switch design:



Model mechanism

RNA Polymerase (RNAP) binds to a promoter leading to transcription of a complete mRNA molecule

Combining open-complex formation and N-elongation steps gives

$$P + N \dashrightarrow C_c \dashrightarrow P + N + M_N$$

Where P is the RNAP, N is the promoter, C_c is the closed transcription complex, M_N is the mRNA molecule of nucleotide length N.

Additional kinetic assumptions:

• Concentration of promoters << concentration of RNAP ==> quasi-steady state assumption can be applied

• Degradation of mRNA by cellular Rnases

•Similar kinetics for translation of mRNA into functional proteins

•Add repression by assuming that the repressor protein binds competitively with RNAP to the promoter site, may be a multimer, and may bond cooperatively

•Quasi-steady state assumption for mRNA synthesis

•Nondimensionalize the equations

Macroscopic, deterministic kinetic equations

$$\frac{d\,u}{d\,t} = \frac{\alpha}{1+\rho_1 v^{\beta}} - u$$

$$\frac{d\,v}{d\,t} = \frac{1}{1+\rho_2 u^{\gamma}} - v$$

u = (scaled) concentration of protein 1
α = effective synthesis rate of protein 1
ρ_1 = concentration of promoter of protein 2
β = cooperativity of promoter of protein 2
v = concentration of protein 2
ρ_2 = concentration of promoter of protein 1
γ = cooperativity of promoter of protein 1

$$\frac{d\,u}{d\,t} = \frac{\alpha}{1+\rho_1 v^{\beta}} - u$$

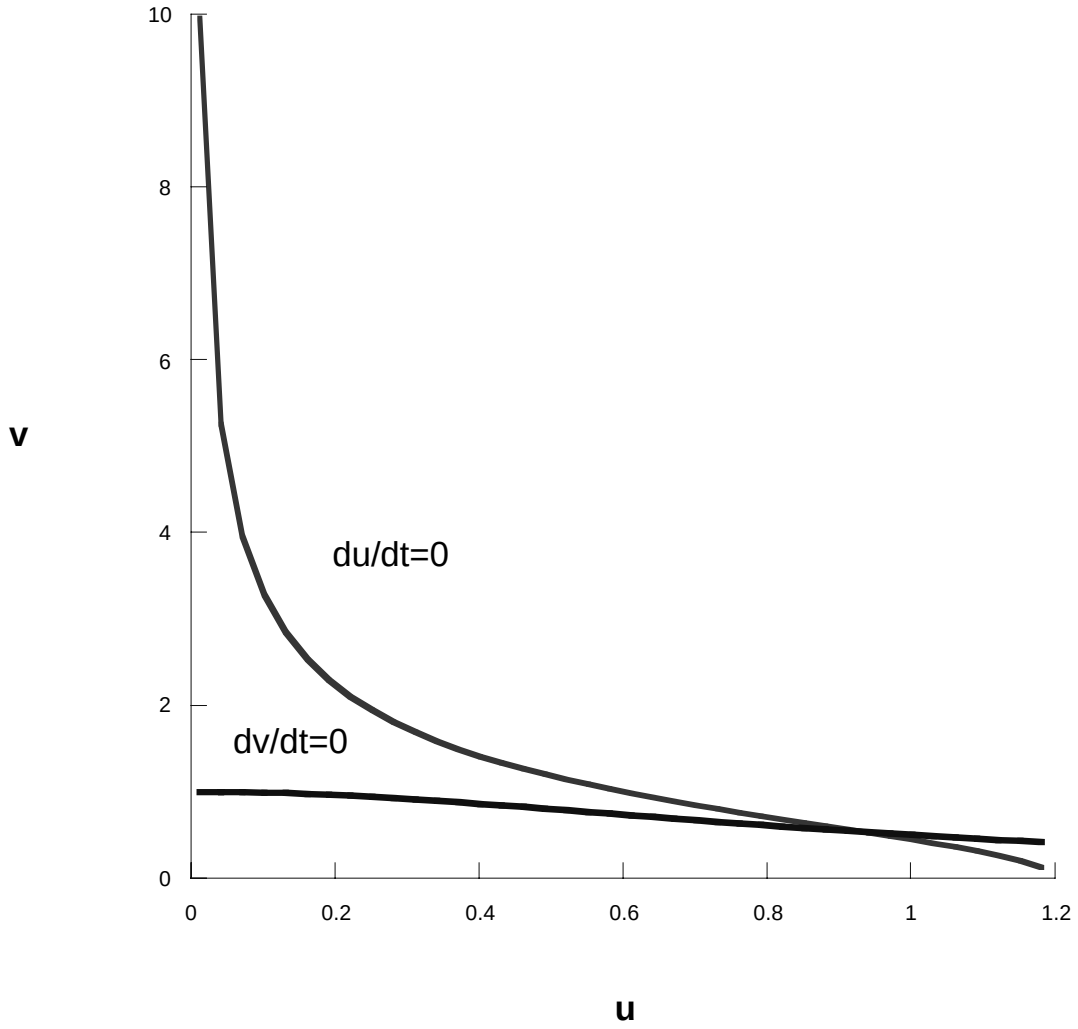
$$\frac{d\,v}{d\,t} = \frac{1}{1+\rho_2 u^{\gamma}} - v$$

Fundamental aspects:

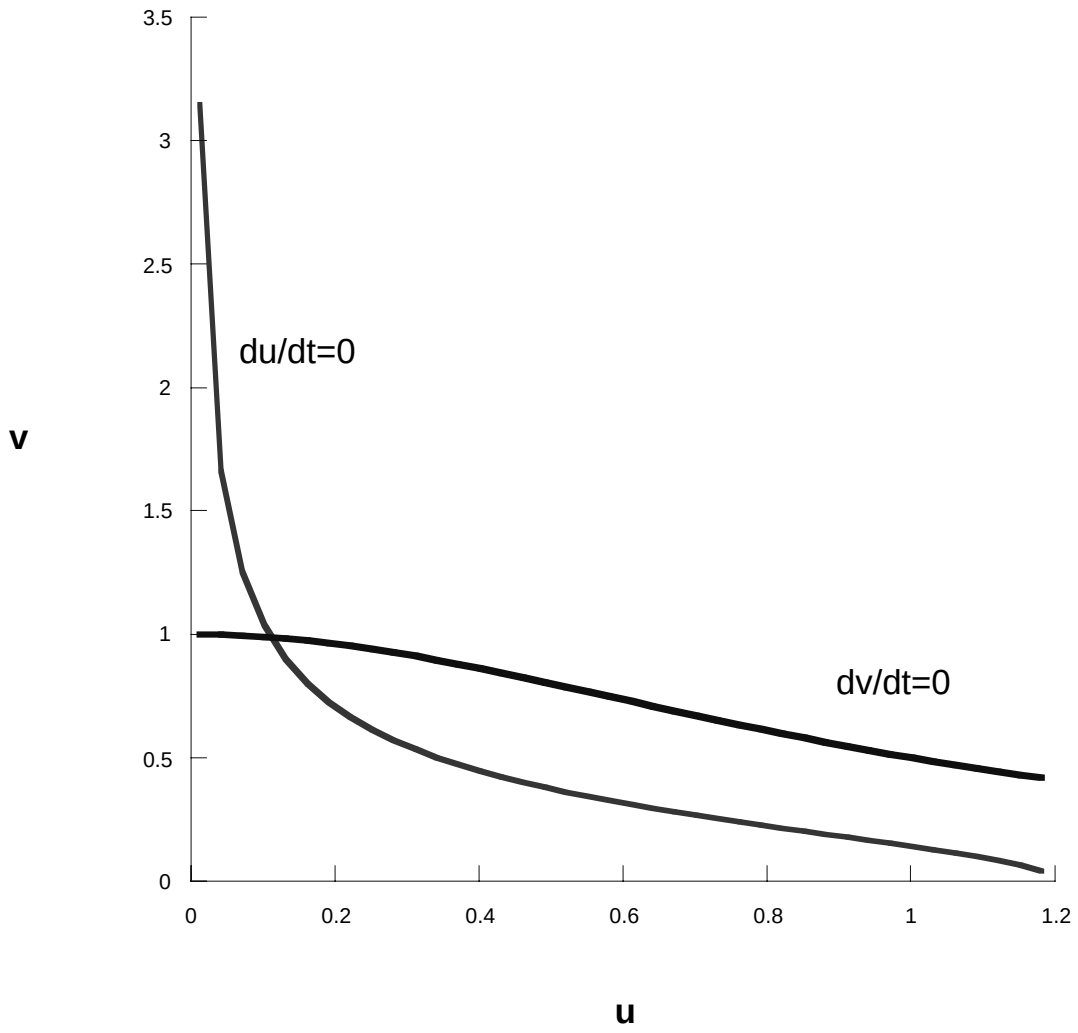
- Cooperative repression (first term)
- Degradation (second term)

Next step: Phase plane analysis as parameters vary. Four possible phase planes

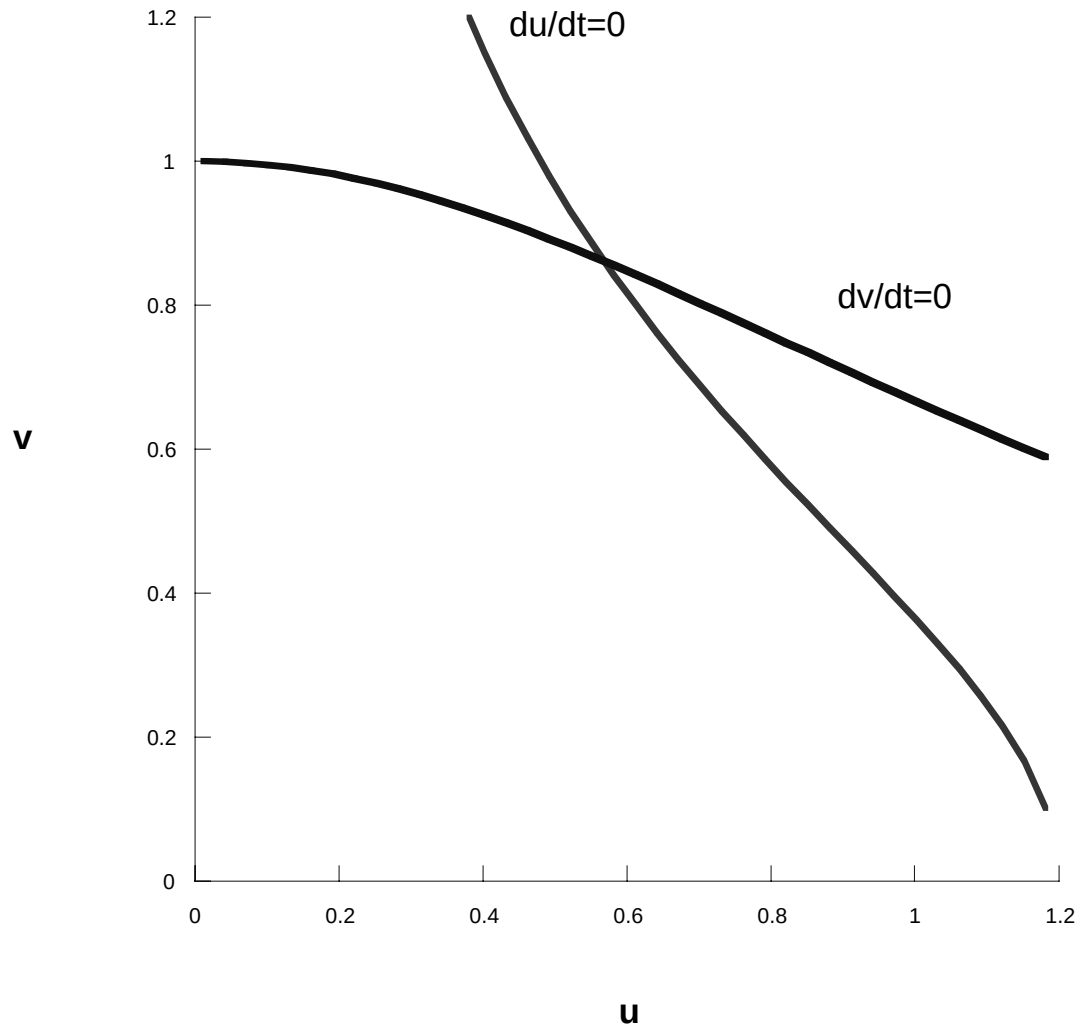
Case 1: High u, low v steady state



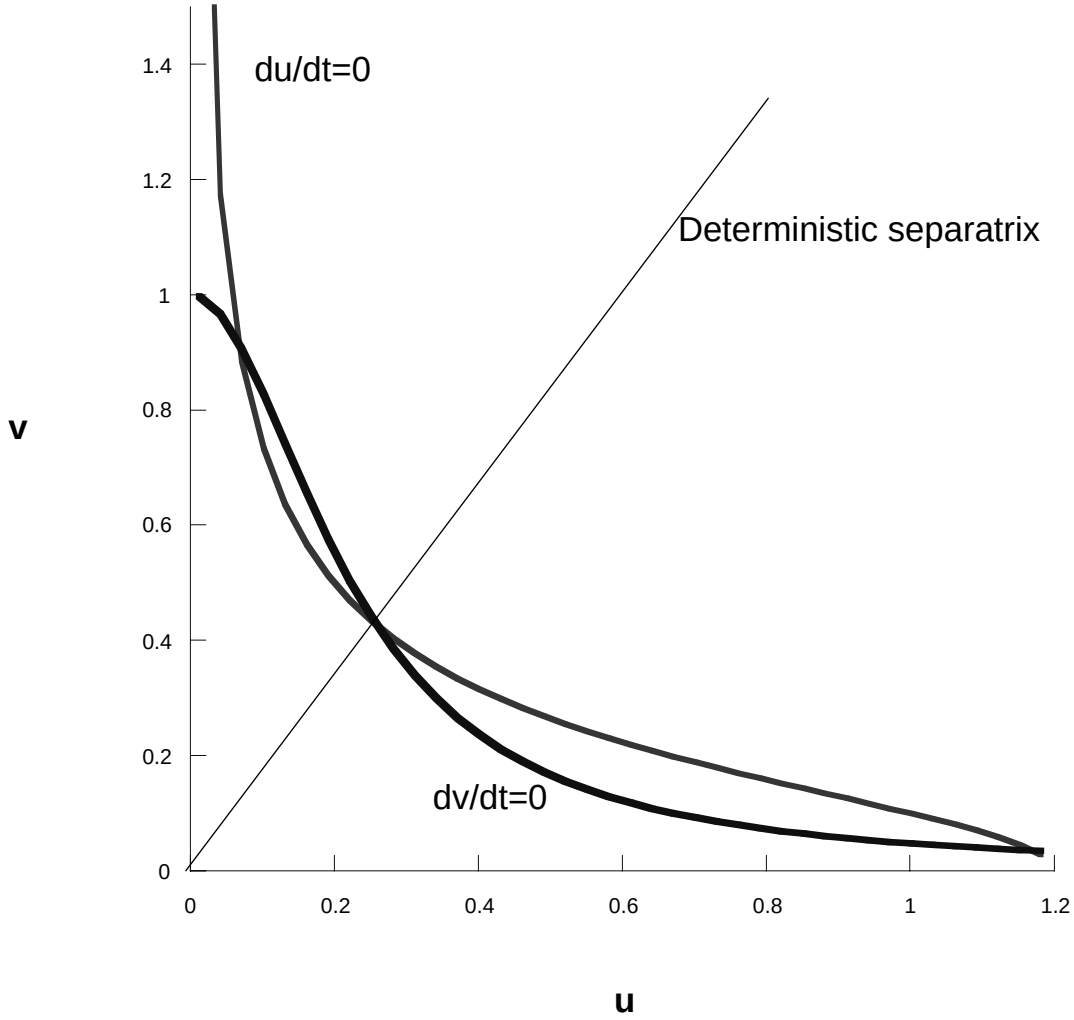
Case 2: Low u, high v



Case 3: Intermediate mixture



Case 4: Two stable points (two phenotypes) and an unstable (saddle point)



Question: Can multi-stability be found in biochemical systems?
Answer: Yes.

Gardner et al. 2000. -- toggle work

H. Degn 1979. Bistability caused by substrate inhibition of peroxidase in an open reaction system. Nature 217:1047

$$S + E \text{ ---> } ES$$

$$ES \text{ ---> } E + P$$

$$S + ES \text{ <---> } ES_2$$

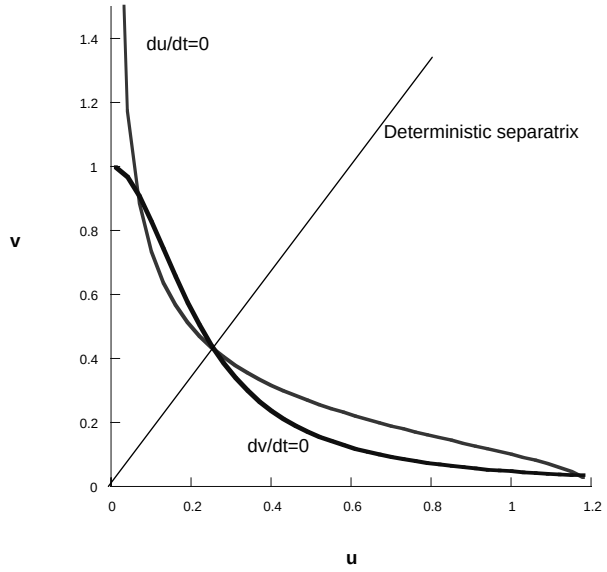
If this takes place in a stirred solution, exchanging substrate by diffusion with a reservoir of constant concentration, then enzyme kinetics lead to multi-stability.

L F Olsen and H Dengn. 1977. Chaos in an enzyme reaction. Nature 267:177-178

“Saddle-node” bifurcation

Question: If there are molecular fluctuations present, and one or more parameters changes so that the phase plane changes from a stable node to a saddle point, where will the system end up and with what probability?

Deterministic answer:



What is the effect of fluctuations?

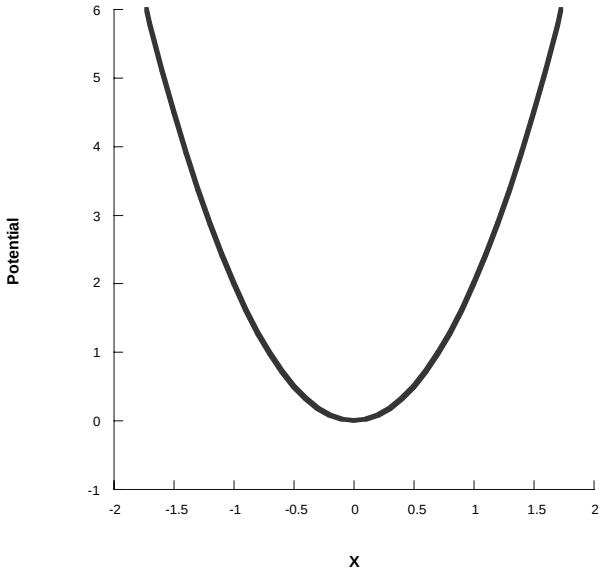
Evolutionary Theories of Aging

There exist specialized age-of-onset modifier genes which repress the action of other genes that are deleterious until an advanced age has been reached. Little harm results from the expression of the mutations then, however, and senescence gradually ensues with their de-repression. In this theory, selection modifies life span by simply increasing or decreasing the period over which such modifiers are effective.

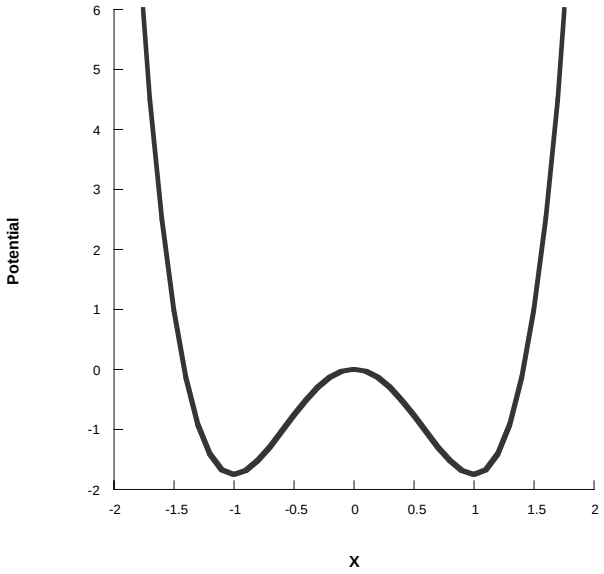
Senescence effector genes are held in check early in life by senescence repressor genes

Also see CE Finch and TBL Kirkwood. 2000. *Chance, Development, and Aging*. Oxford University Press.

Warm-up: Stochastic Dynamics of a Particle in a Potential Well



Parameter changes ---------->



$$dX = Xdt + \sqrt{2\varepsilon}\, dW$$

X restricted to [-1,1]

W(t) = Brownian motion:

W(t) is continuous

dW Gaussian distributed with $E\{dW\} = 0$, $E\{dW^2\} = dt$

ε determined by the fluctuation dissipation theorem

Fundamental probability:

$$u(x) = \Pr\{ X(t) \text{ reaches 1 before -1, given that } X(0) = x\}$$

Master Equation

$$u(x) = E_{dX}\{ u(x+ dX) \}$$

“In the right hands, integration by parts and Taylor expansion are still among the most powerful tools in applied mathematics” (Mark Kac)

$$u(x)= E_{dX}\{ u(x) + dX \frac{du}{dx} + \frac{1}{2} (dX)^2 \frac{d^2u}{dx^2} + ...\}$$

$$= u(x) + E_{dX}\{dX\} \frac{du}{dx} + \frac{1}{2} E_{dX}\{(dX)^2\} \frac{d^2u}{dx^2} + ...$$

Take expectations

$$u(x) = u(x) + x\,dt\,\frac{du}{dx} + \frac{1}{2}(2\varepsilon)dt\,\frac{d^2u}{dx^2} + o(dt)$$

Divide by dt and take the limit as dt-->0

$$x\,\frac{du}{dx} + \varepsilon\,\frac{d^2u}{dx^2} = 0$$

Solve this equation with boundary conditions

$u(1) = 1$

$u(-1) = 0$

$$u(x) = \frac{\int_{-1}^{x} \exp(-\frac{y^2}{2\varepsilon})\,dy}{\int_{-1}^{1} \exp(-\frac{y^2}{2\varepsilon})\,dy}$$

Change variables, do the asymptotic expansion

$$u(x) \sim g_0\, \Phi(\frac{x}{\sqrt{\varepsilon}})$$

where

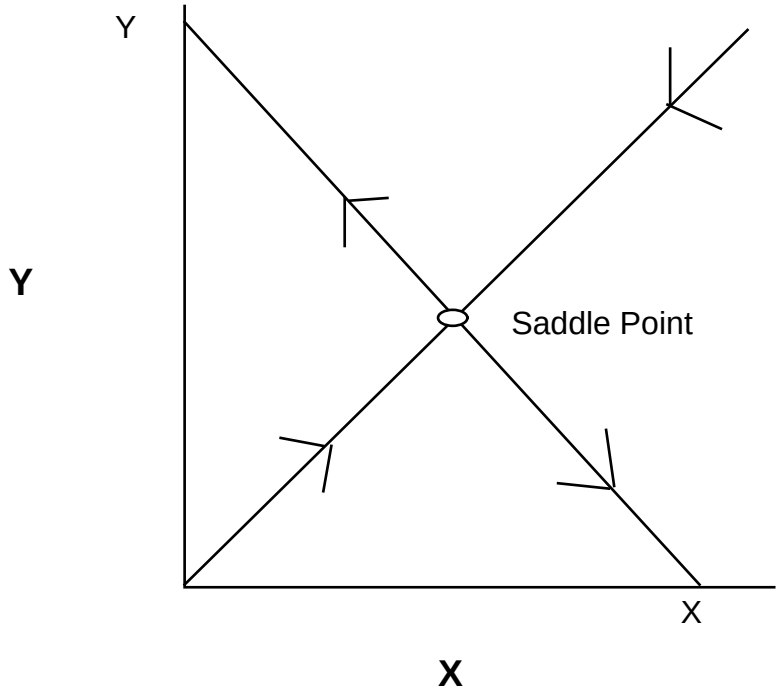
$$\Phi(x) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{x} \exp(-s^2/2)\ ds$$

The two dimensional case

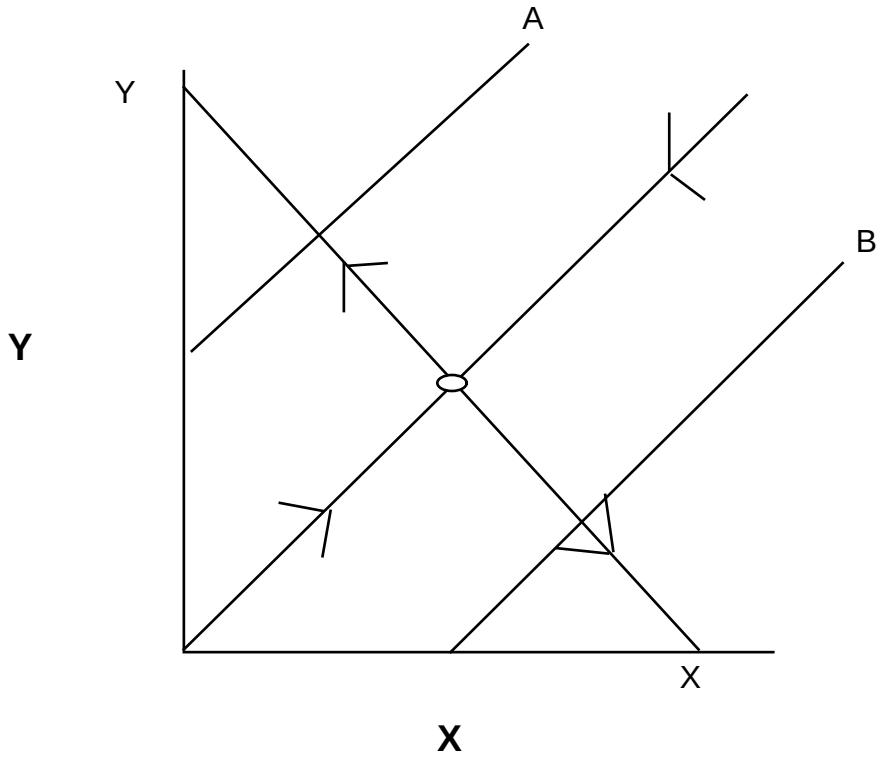
$$dX = b_1(X,Y)\,dt + \sqrt{\varepsilon a_{1\,1}(X,Y)}\,dW_1 + \sqrt{\varepsilon a_{1\,2}(X,Y)}\,dW_2$$

$$dY = b_2(X,Y)\,dt + \sqrt{\varepsilon a_{1\,2}(X,Y)}\,dW_2 + \sqrt{\varepsilon a_{22}(X,Y)}\,dW_3$$

Underlying deterministic phase plane



The two dimensional probabilistic question



u(x,y) = Prob{ the trajectory (X(t),Y(t)) crosses A before B, given that X(0)=x, Y(0)=y}

Proceed with the same kind of expansion of the Master Equation

$$0 = \frac{\varepsilon}{2}\{\, a_{11}(x,t)\,\frac{\partial^2 u}{\partial x^2} + 2\, a_{21}(x,t)\,\frac{\partial^2 u}{\partial x \partial y} + a_{22}(x,t)\,\frac{\partial^2 u}{\partial y^2}\}$$

$$+ \; b_1(x,t)\,\frac{\partial u}{\partial x} + \; b_2(x,t)\,\frac{\partial u}{\partial y}$$

Boundary conditions

$$u(x,y) = 1 \quad \text{if} \quad (x,y) \text{ on } A$$

$$u(x,y) = 0 \text{ if} \quad (x,y) \text{ on } B$$

WKB(J) Solution (analogy: semiclassical mechanics)

$$0 = \frac{\varepsilon}{2}\left\{ a_{11}(x,t)\,\frac{\partial^2 u}{\partial x^2} + 2\,a_{21}(x,t)\,\frac{\partial^2 u}{\partial x \partial y} + a_{22}(x,t)\,\frac{\partial^2 u}{\partial y^2}\right\}$$

$$+ b_1(x,t)\,\frac{\partial u}{\partial x} + b_2(x,t)\,\frac{\partial u}{\partial y}$$

Assume that

$$u(x,y) = g_0\,\Phi\left(\frac{\psi(x,y)}{\sqrt{\varepsilon}}\right) + O(\sqrt{\varepsilon})$$

Where g_0 and $\psi(x,y)$ are to be determined

Do an asymptotic expansion in powers of ε

$$u(x,y) = g_0\,\Phi\left(\frac{\psi(x,y)}{\sqrt{\varepsilon}}\right) + O(\sqrt{\varepsilon})$$

$$\text{If } \Phi(z) = \frac{1}{\sqrt{2\pi}} \int_{-4}^{z} \exp(-s^2/ds)$$

then

$$\frac{d}{dz}\Phi(z) = \frac{1}{\sqrt{2\pi}} \exp(-z^2/2)$$

and

$$\frac{d^2}{dz^2}\Phi(z) = \frac{1}{\sqrt{2\pi}}(-z)\exp(-z^2/2) = -z\frac{d}{dz}\Phi(z)$$

$\psi(x,y)$ satisfies the eikonal equation

$$b_1(x,y)\frac{\partial\psi}{\partial x} + b_2(x,y)\frac{\partial\psi}{\partial y} - \frac{1}{2}\{ a_{11}(x,y)\psi(x,y)\left(\frac{\partial\psi}{\partial x}\right)^2 + 2a_{12}(x,y)\psi(x,y)\frac{\partial\psi}{\partial x}\frac{\partial\psi}{\partial y} + a_{22}(x,y)\psi(x,y)\left(\frac{\partial\psi}{\partial x}\right)^2 \}=0$$

Introduce a new function

$$\theta(x,y) = -\frac{1}{2}\psi(x,y)^2$$

Eikonal equation becomes

$$b_1(x,y)\frac{\partial\theta}{\partial x} + b_2(x,y)\frac{\partial\theta}{\partial y} + \frac{1}{2}\{ a_{11}(x,y)\left(\frac{\partial\theta}{\partial x}\right)^2 + 2a_{12}(x,y)\frac{\partial\theta}{\partial x}\frac{\partial\theta}{\partial y} + a_{22}(x,y)\left(\frac{\partial\theta}{\partial x}\right)^2 \}=0$$

Solution of eikonal equation

$$b_1(x,y)\frac{\partial\theta}{\partial x} + b_2(x,y)\frac{\partial\theta}{\partial y} + \frac{1}{2}\{ a_{11}(x,y)\left(\frac{\partial\theta}{\partial x}\right)^2$$

$$+ 2a_{12}(x,y)\frac{\partial\theta}{\partial x}\frac{\partial\theta}{\partial y} + a_{22}(x,y)\left(\frac{\partial\theta}{\partial x}\right)^2 \}=0$$

Solved by the method of characteristics; associated Hamiltonian, Lagrangian and variational principle

$$H(x,y,p,q) = (1/2)\{ a_{11}(x,y)p^2 + 2\, a_{12}(x,y)pq + a_{22}(x,y)q^2\} + b_1(x,y)p + b_2(x,y)q$$

Trajectories generated according to

$$dx/ds = \partial H/\partial p \qquad dy/ds = \partial H/\partial q$$

s ~ ‘ray’ along which probability is transported

Alternative: transform to coordinates tangential and normal to the separatrix; eikonal equation becomes a nonlinear ODE

Lagrangian defined by

$$H(x,y,p,q) + L(x,y,dx/ds,dy/ds) = p\, dx/ds + q\, dy/ds$$

and is

$$L(x,y,dx/ds,dy/ds)$$

$$= (1/2)a_{11}(x,y)(b_1(x,y) - dx/ds)^2 + a_{12}(x,y)(b_1(x,y) - dx/ds)(b_2(x,y)-dy/ds)$$

$$+(1/2)a_{22}(x,y)(b_2(x,y) - dy/ds)^2$$

$a(x,y)$ is the inverse of the variance-covariance matrix a(x,y).

Hamilton-Jacobi Theory

$\theta(x,y)$ is the minimum of the integral of the Lagrangian taken over all paths joining the point (x,y) and a given initial point (x_0,y_0).

If (x_0,y_0) is chosen to be the saddle point then the Lagrangian=0, $\theta(x,y)=0$, so $\psi(x,y)=0$ on the separatrix.

One can now find $\psi(x,y)$ by integrating the Hamilton-Jacobi equations.

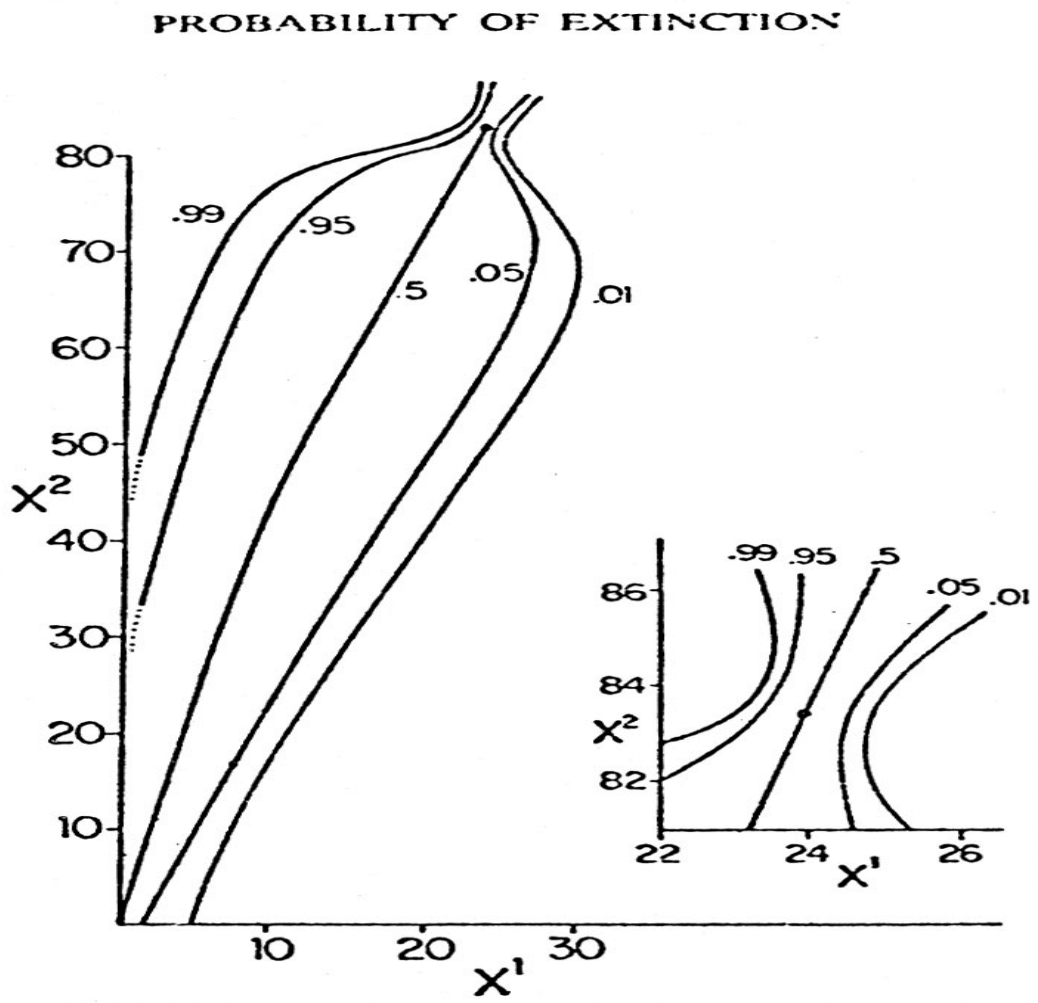
Optical analogy

Solutions of the Hamilton-Jacobi equations represent all possible trajectories in the space of the stochastic flow, analogous to rays in optics. Along these trajectories, probability is transported, according to the equation for θ. This is analogous to the transport of intensity of light along the optical rays.

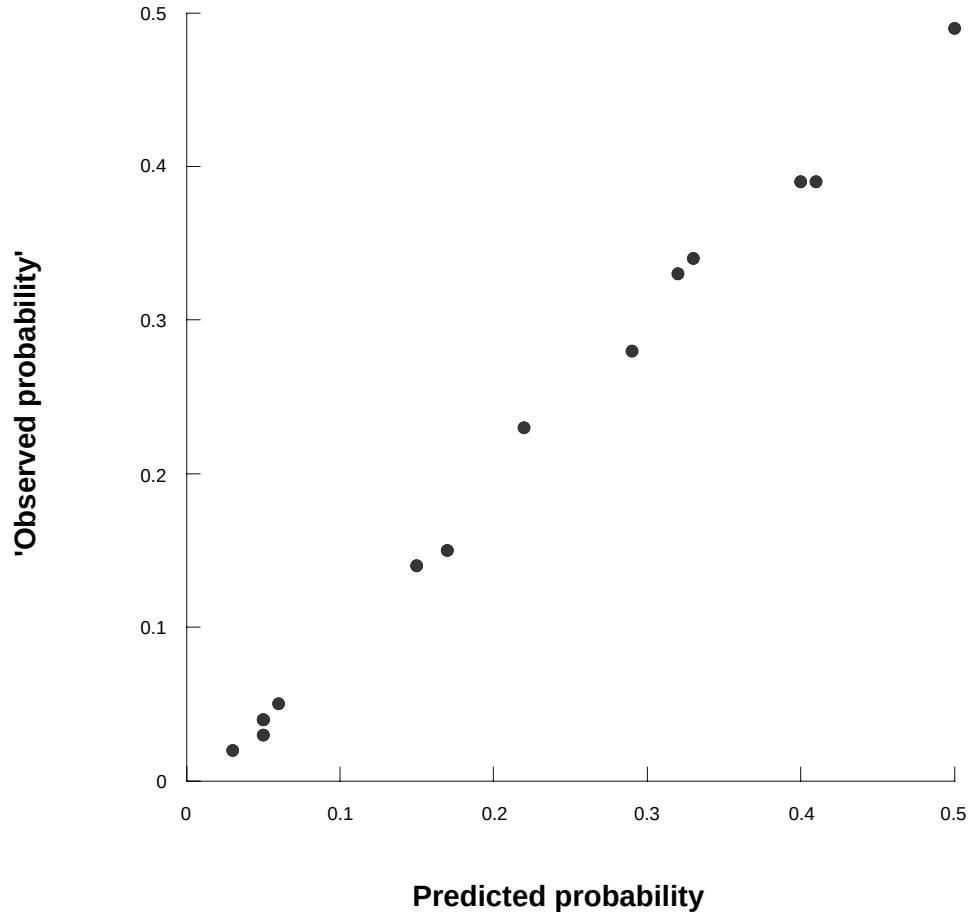
As with diffraction, for which a ray theory predicts shadow transition zones, this theory predicts probability contours. Diffraction theory leads to Fresnel integrals, stochastic populaion theory to Gaussian integrals (or their generalization, Airy, Pearcey).

Output of the theory is probability contours

(Mangel and Ludwig.1977. SIAP 33:256)

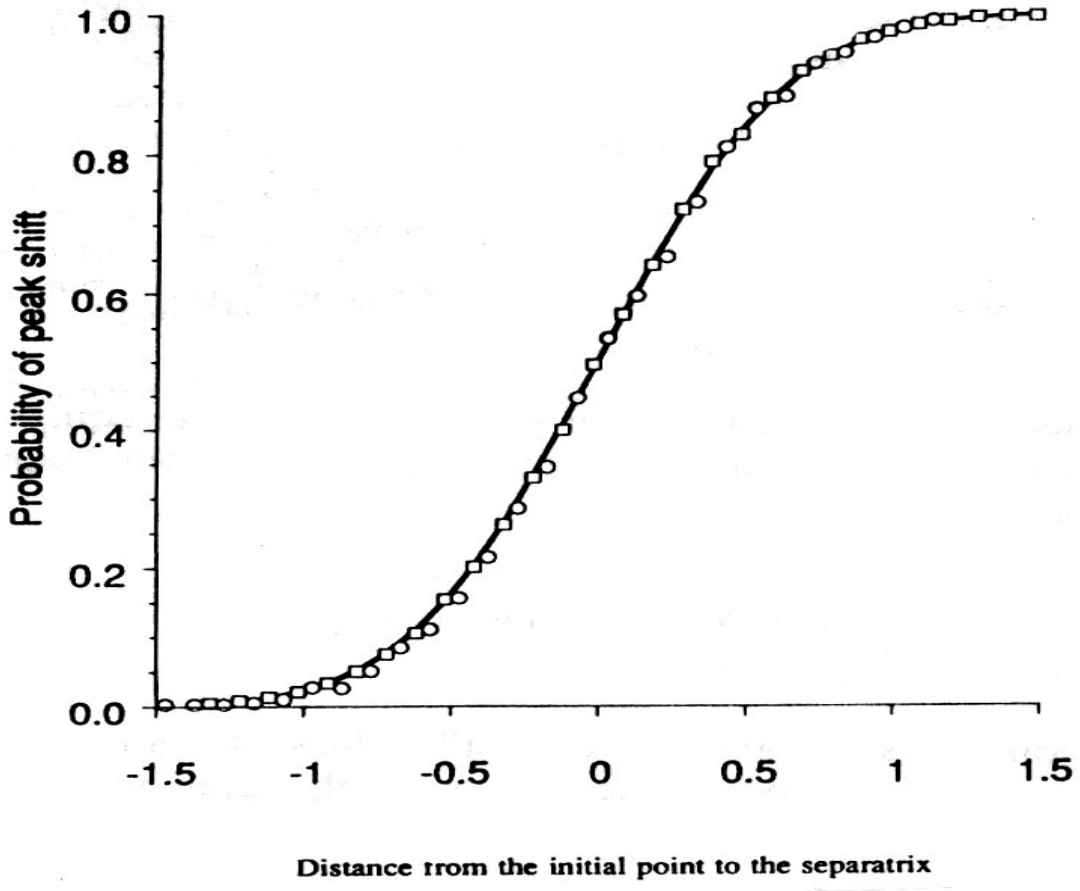


Comparison of the theory and Monte Carlo simulations of the stochastic process



Mangel and Ludwig.1977. SIAP 33:256; Mangel. 1978, JCP 69:3697

Third party test of the theory (solid line) with Monte Carlo experiments (circles, squares)



Price, T., Turelli, M., and M. Slatkin. 1992. Evolution 47:280-290.

Some comments (M. Mangel. 1994. Theoretical Population Biology. 45:16)

• Can do the same thing even if there is no underlying macroscopic deterministic system

$\rho_{ij}(x,y) =$

$$\text{Prob}\{ X(t+1) = x + \varepsilon i, Y(t+1) = y + \varepsilon j \mid X(t) = x, Y(t) = y \}$$

• Origin and validity of diffusion approximations to the master equation

• Emergence of macroscopic dynamics from stochastic processes.

Deterministic, macroscopic equations are a sub-set of the solutions of the Hamilton-Jacobi equations

Coincidence or Convergence?

(Simberloff, D. 1980. A succession of paradigms in ecology: essentialism to materialism and probabilism. Synthese 43:3-39)

1859

Darwin: *Origin of the Species*

Maxwell: kinetic gas law.

These are the foundations for non-deterministic thinking in biology and physics.

“Our understanding of population phenomena will require stochastic treatment”

Three levels of indeterminacy

i) Molecular indeterminacy (e.g. random mutations in the genome)

ii) Chaotic behavior of deterministic nonlinear systems

iii) Indeterminacy engendered by the enormous number of objects in the biological system

“The probabilistic revolution is far from complete and the variability [that] typifies ecological systems because of their complexity...suggests different mathematical approaches and criteria for success” (pg. 27).

The central problem of cell biology now is not so much the gathering of information, but the comprehension of it. What remedy can there be for that state of affairs?

...models help make a coherent story from disparate sets of data that benefits not only practitioners, but bystanders as well. And models are also pointers to the design of experiments that test current understanding incisively. *Cell biologists' collective neglect of modeling has become a grievous handicap…How long will it be before that prejudice is banished in the face of the imperatives of understanding*?

J. Maddox. 1998. *What Remains to be Discovered?* Simon and Schuster, New York (pg189, 193)

