Spatially-Distributed Biological Processes
Reaction-Diffusion Equations

Lecture 21
All biological processes take place in time and **space**

Until now all the processes you’ve been discussing in this course were implicitly assumed to take place only in time but not in space. In other words, any system was assumed to be spatially homogenized so that all physical conditions in one location were identical to those in any other location. In chemical engineering this phenomenon is called “constantly stirred tank reactor” or simply CSTR.

Biological systems however are not stirred tank reactors. In fact we recognize biological systems as possessing complex internal structure and capable of formation of intricate patterns on all levels of organization from individual cell to the large scale patterns exhibited by populations. The process of emergence of biological patterns and structure, morphogenesis, has attracted curiosity of scientists throughout the entire history of humankind. However only in the past century our experimental and theoretical methods reached necessary complexity and precision to tackle the burning question of how biological structures emerge. Conceptually, as a result of this inquest we arrived at two seemingly contradictory conclusions. Firstly, there is nothing mystical about the biological processes – they are governed by all the same principles as been discovered in physical and chemical sciences. Secondly, we continue to discover deeper and deeper levels of complexity which never stop to bewilder us.

In this part of the course we will explore in some detail both the methods for quantitative understanding of biological patterns and spatial order as well as some exemplary biological systems whose complexity leaves us in awe and admiration for the endless creativity of nature.
**Things move around – Simple diffusion and Fick’s law**

Mass conservation law in a one-dimensional case (simply math):

\[
Sdx \cdot \frac{\partial c(x,t)}{\partial t} = S \cdot (J(x,t) - J(x + dx,t))
\]

\[
\frac{\partial c(x,t)}{\partial t} = -\frac{\partial}{\partial x} J(x,t)
\]

Fick’s law, on the other hand, is an empirical observation connecting flux and the gradient of concentration:

\[
J(x,t) = -D \frac{\partial}{\partial x} c(x,t)
\]

Together the two equations result in a well-known diffusion equation:

\[
\frac{\partial^2 c(x,t)}{\partial x^2} = \frac{\partial}{\partial x} \left(-D \frac{\partial c(x,t)}{\partial x}\right)
\]

Practically important generalization includes local creation and destruction of chemical species – chemical reactions:

\[
\frac{\partial c(x,t)}{\partial t} = D \frac{\partial^2 c(x,t)}{\partial x^2} + f(c,x,t)
\]

One common method of quantitative description for spatially inhomogeneous systems which has enjoyed wide and successful applicability is through the use of partial differential equations known as reaction-diffusion equations. These equations are a natural extension for a spatially distributed case of the mass-action rate laws you have studied in the previous lectures. In the course of the following derivation, the system of ordinary differential equations \( \frac{dc}{dt} = f(c,t) \) gets replaced by the system of partial differential equations taking into the consideration the random motion of the molecules in space.

Indeed, let us consider a one-dimensional case which can be imagined as a very thin and long capillary such that its diameter is several orders of magnitude smaller than its length. Let us at first assume that molecules are allowed to randomly move in the aqueous solution and no reactions take place. In this case for a small volume \( Sdx \) the change of masses of chemical species \( c \) is given by the difference of flow of molecules through the cross section of the capillary at the points \( x \) and \( x + dx \) respectively. As usually in the calculus derivations we assume a limit \( dx \rightarrow 0 \) and thus obtaining the second equation which connects change in concentration with the flux of molecules. Until now we used only the mass conservation law. Now we need a relationship between concentration and the flux which is conveniently provided by the Fick’s law. Please note that this law is an empirical fact and as such (as normally in physical sciences) is a result of an approximation. The proportionality coefficient between the gradient of concentrations and the flux is a well-known to you diffusion coefficient usually measured in cm²/s and an important property of a molecule.

Finally substituting Fick’s law into the mass conservation equation we obtain a standard diffusion equation. If now we go one step further by combining molecular fluxes with local reaction kinetics in the mass conservation equation, we finally obtain a reaction-diffusion equation. In simple terms it states that the change in local concentrations of chemical species is a result of local reaction and diffusion transport. Although this statement sounds banal, it provides in important intuition into the understanding of behavior of the RDE from knowing the behavior of the corresponding ODEs.
Solution of the diffusion equation and diffusion coefficient

Simple diffusion equation can be solved exactly in any number of dimensions $d$:

$$c(x,t) = \frac{c_0}{(4\pi Dt)^{0.5d}} \exp \left( -\frac{x^2}{4Dt} \right)$$

The resulting solution is a Gaussian curve with a time-dependent dispersion.

From this we can obtain the root-mean-square displacement of a diffusing particle in one dimension:

$$\langle x^2 \rangle = \int_{-\infty}^{\infty} x^2 \cdot c(x,t) dx = 2Dt \rightarrow \sqrt{\langle x^2 \rangle} = x_{rms} = \sqrt{2Dt}$$

In three dimensions this result converts into:

$$x_{rms} = \sqrt{6Dt}$$

This result is also can be rewritten in the form convenient for calculation of time necessary to travel certain distance $R$:

$$t = \frac{R^2}{6D}$$

The simple diffusion equation can be analytically solved on the entire space for any dimensionality of the latter. Let us here look at the behavior of the one-dimensional case as the only difference is the exponent in the factor of the solution. The initial conditions are assumed to be a Dirac delta-function with location in 0. In this case diffusion describes spreading of the initial mass of molecules over the entire space represented by the family of Gaussian curves with time-dependent amplitude and dispersion. This solution provides an intuitive qualitative picture of diffusion as a process always responsible for the smoothing of all the existing chemical gradients. However, this intuitive assumption does not hold in all cases when diffusion is combined with the reaction. In the following lectures we will consider examples of the situation where the role of diffusion is totally opposite as it induces formation of a spatial pattern.

One important application of the analytical solution of the diffusion equation is the estimation of an average displacement of a diffusing particle with time. From statistical physics it follows that the average quadratic displacement of the particle starting at the moment $t=0$ at the point $x=0$ is given by the integration of the product of $x^2$ and the probability density function describing motion of particles. The messy integral converges into a surprisingly concise and simple expression. This result is very important and is commonly used to estimate either the time necessary for a particle to cover a given distance or conversely to estimate the distance the particle would run after a given time. Now to use this result in practice we need to estimate the value of the diffusion coefficient $D$. 
What defines the diffusion coefficient $D$

Theoretic estimates for the coefficient of diffusion can be obtained from the Einstein's theory of Brownian motion:

$$D = \frac{kT}{f} = kTb$$

For spherical particles with radius $r$:

$$D = \frac{kT}{6\pi\mu r}$$

Finally the radius of a molecule can be estimated from its molecular weight and density:

$$M = \frac{4}{3}\pi r^3 N_A \rho \rightarrow D = \frac{kT}{3\mu} \left( \frac{\rho N_A}{6\pi^2 M} \right)^{\frac{1}{3}} \rightarrow DM^{\frac{1}{3}} = \text{const}(T)$$

For small molecules ($M < 1000$) dependence on the cubic root of molecular weight needs to be replaced by the square root dependence:

$$DM^{\frac{1}{2}} = \text{const}(T)$$

What defines the diffusion coefficient of a molecule? The answer to this question comes from physical theory of Brownian motion developed by A. Einstein in 1905. Firstly, diffusion of a molecule can be considered as a result of collision with molecules of solvent, water in the biologically relevant cases. This means that the diffusion will be dependent on the thermal properties of the solution and indeed, $D$ was found to grow linearly with temperature. For large molecules, such as most of the proteins, the problem can be reduced to the one of a sphere with radius $r$ which is much larger than the size of molecule of water. In this case the viscous frictional coefficient $f$ or its inverse – mobility $b$ can be expressed through the viscosity of the solvent and the radius of the sphere. The radius of protein molecules can be estimated from their molecular weight assuming that the density of proteins is approximately the same and equal to 1.3-1.4 g/cm$^3$. From this theory it follows that for large molecules and particles, diffusion coefficient scales as an inverse cubic root of the molecular weight.

Different theoretical considerations applicable for the small molecules, bring us to the conclusion that the diffusion coefficient of small molecules is inversely proportional to the square root of the molecular weight.

To demonstrate the order of magnitude, some of the standard diffusion coefficients are shown in the table. Please note however that the values were obtained in the in vitro system, moreover, in the dilute aqueous solutions. Despite the fact that intracellular environment is very far from the dilute aqueous solutions, these values of diffusion coefficients were repeatedly used for estimation of traveling times of molecules inside the cell for decades. Thus one very well-reputable textbook claims: “This shows that even the heaviest molecules normally found in cells travel across a cell in a second or so, and achieve a more or less uniform distribution in the cytoplasm”. We will revisit this statement two lectures from now.
Let us now consider one special case of diffusion which is important from both the biological point of view and is illustrative from the mathematical viewpoint. Namely, a diffusion through a membrane. Many low molecular weight non-polar molecules like steroid hormones can in fact diffuse through a cell membrane in both directions. Although in eukaryotes this type of cell signaling is rather deprecated as essentially obsolete and is largely substituted by receptor-ligand mechanisms, this method is in active use by bacteria who first invented it. For example, free diffusion of signaling molecules called homoserine lactones is an essential mechanism of the phenomenon of quorum sensing allowing bacteria to feel the presence of siblings and even other bacterial species in the medium.

As a very simple case let us consider outward diffusion of a substance Z present in the cell and outside in some constant but unequal concentrations. In a steady state, which will be the matter of our analysis, dc/dt is zero and from the diffusion equation it follows that the flow J is constant. Using boundary conditions inside and outside of cell, we find that the concentration of Z must change linearly throughout the membrane length to satisfy the diffusion equation and provide a constant flux. The coefficient of proportionality between the flux J and the difference of concentrations – D/L- is called membrane permeability. The numeric values of permeability for a number of low weight molecules and a bacterial cell wall are given in the table (from ). Just like the diffusion coefficient D, P scales as inverse square root for small molecules and as inverse cubic root for heavy molecules (M > 100).
Formation of patterns in distributed media with diffusion

Real World

Spatio-temporal patterns in distributed systems

Model World

Spatially heterogeneous solutions of RD equations

**Fundamental question:** can we infer the behavior of the RDE from the known dynamics of spatially homogeneous system?

**The answer:** Yes and No. There is no universal relationship between the behavior of RDE and adjoining ODE.

**Intuition:** spatially distributed system is the collection of diffusion-coupled homogeneous volumes

With the discussion of diffusion through the membranes we are done with our brush-up on the physical chemistry. From now on, we are going to consider behavior of spatially distributed systems whose linear dimension $L$ significantly exceeds the characteristic scale of diffusion $L_d$ ($L \gg L_d$). Such systems are capable of creating and supporting complex spatio-temporal dynamics. In the following part of the course we going to constantly jump from the real world to the world of mathematical models often using the terminology intermittently. Therefore, it is important to make clear the correspondence of terms. Once we decided to model real systems with RDEs, the spatially heterogeneous solutions of them $u(x,t)$ are going to represent spatio-temporal patterns observed in experiment. If the model has adequate complexity and is “correct”, there is usually at least qualitative one-to-one correspondence between the experimentally observed phenomena and the solutions of equations. If the remove diffusion term in the RDE and exchange the time partial derivative by ordinary, we will get adjoining system of ODEs. Conversely, any systems of mass-action law equations can be converted into RDE by adding diffusion terms.

Obviously, analysis of ODEs is considerably easier than analysis of partial differential equations. Therefore, we would be very much interested to learn how the system of RDEs behaves from the knowledge of ODE dynamics. Unfortunately, in general case there is no mathematical formalism providing this connection. Intuitively, we expect to see a relationship which based on the fact that spatially distributed system can be considered as large, infinite in the limit, array of diffusively coupled elementary volumes of size $L_e \ll L_d$. Then each of such volumes would be a well-stirred reactor with homogeneous distribution of concentrations. This approximation is the way how we numerically simulate RDEs and is sometimes also useful for the intuitive understanding of the RDE dynamics.

In the following, we start with the systems where RDE dynamics can be envisaged from the adjoining ODEs and then arrive at an important examples of the systems where the contribution of diffusion is not intuitive by all means.
So we start our exploration of the patterns in spatially distributed systems. It is clear that the best way to do this is to start with systems where our intuition is of more help and proceed to the more weird systems once we developed some basics. Our first stop is multistable systems. Here you can see the phase portrait of an ODE system with three stable states. The topology of the phase space requires that each two stable states are separated by an unstable manifold which plays a role of the watershed separating basins of attraction for the attracting (stable) states or simply put attractors. What happens if we convert the ODE into RDE by adding diffusion terms? It appears intuitively clear that if the medium at every point has values corresponding to a stable state that should be a solution for an RDE as well, that is homogeneous solution. Here however there is some very important caveat, this intuitive picture is only true if there is no so-called diffusion-driven or Turing instability which may result in the formation of spatial patterns out of the homogeneous condition. We will consider this later in the course and for now assume that stability of the homogeneous state is granted. What happens if a contiguous part of the medium is in one stable state while other parts are in different stable states?

Again, let us start from a simple and intuitively clear case. Consider one variable system and one spatial dimension. The system is called Fisher equation. It was simultaneously described by Kolmogoroff, Pokrovsky and Piskunoff and therefore I will refer to it as FKPP equation. It describes propagation of a species on an infinite habitat. The local dynamics is characterized by linear growth and quadratic self-inhibition terms typical for so-called Maltusian description of population dynamics. Clearly, the solution $u=1$ (area populated) is stable while $u=0$ (area empty) is unstable. It has been shown that the state of full occupancy $u=1$ propagates as a wave with a profile shown on the slide. It is customary to characterize the wave profile with a front width – the width of the coordinate span on which the function changes from one state to another. Not that the spatial derivative of the front profile is appreciably different from 0 only on the width of the front.
Finding waves in RDE systems: the $z=x-ct$ trick

Traveling waves are defined as solutions $u(x,t)$ with translational symmetry – their spatial profile remains constant while the wave propagates in space. Therefore they are sought after in the form:

$$u(x,t) = U(z),\ z = x-ct$$

Substituting $z$ into FKPP equation we get:

$$DU'' + cU' + kU(1-U) = 0$$

With boundary conditions:

$$U(+\infty) = 1,\ U(-\infty) = 0$$

Converting second order equation into a system of two first order equations we get:

$$U' = V$$

$$DV' = -cV - kU(1-U)$$

Which has two stationary points $(0,0)$ and $(0,1)$. While the second is always a saddle, the first can be a stable node or a stable spiral:

$$c \geq c_{\text{min}} = 2\sqrt{kD}$$ - stable node

$$c < c_{\text{min}}$$ - stable spiral

does not correspond to physically meaningful behavior ($U < 0$)

For any $c \geq c_{\text{min}}$ FKPP equation has one wave solution which corresponds to a heteroclinic solution of the $(U,V)$ system.

What is really a wave? Mathematically, this is a solution of the RDE such that it moves in space and if you consider a coordinate system which moves together with it, the profile of this solution is not changing. In more strict terms it has a translational symmetry. One strange thing about PDEs is that they normally have a continuum of solutions – functions of both time and space. Even more, different classes of functions can be solutions to the same equation! Therefore the same RDEs can support waves and also non-wave solutions. If we are looking for a wave we might look for a specific type of function which has explicit translational symmetry. This is where the trick with looking for a solution depending on a single variable $z=x-ct$ comes from. Once we substitute the $u(x,t)$ by the $U(z)$, all partial derivatives convert into ordinary ones. The constant $c$ in the variable $z$ has a dimension of velocity $x/t$ and is in fact the speed of the wave. Thus we also assume that the speed of the wave we are looking for is not an explicit function of time of space! At first, after substitution of $z$ we need to find which, if any, values of $c$ make sense. Consider again our example, FKPP equation. It is a custom to convert it after substitution into a two-variable system of first order ODEs. Not surprisingly, the stationary states of this system correspond to those of ODEs. What is more curious, only one (!) trajectory of the entire phase space $(U,V)$ satisfies the boundary conditions. This is the heteroclinic solution which starts in saddle state and ends in the stable point. Depending on $c$, this stable point is either node or focus. Since focus would require trajectory to enter negative area which does not correspond to any population density, we discovered that FKPP equation has a minimal velocity of wave propagation. For any $c$ greater or equal to $c_{\text{min}}$, there is one wave solution which satisfies the FKPP equation. As we will see later, this somewhat degenerate case mainly stemming from the fact that FKPP system has only one stable state.
Wave solution in a general bistable RD equation

Systems with two stable states are more common in biological modeling:

\[ \frac{\partial u}{\partial t} = f(u) + D \frac{\partial^2 u}{\partial x^2} \]

If we now employ the usual \( z = x - ct \) trick, we will find:

\[ DU'' = -f'(U) - cU' \]

If we also introduce integral of \( f(U) \) from 0 to \( U - \int f(U) \), then the equation describes a motion of particle with mass \( D \) in the potential \( I(U) \) with friction \( c \):

\[ DU'' = -\partial I/\partial U - cU' \]

The difference of the potential will define the sign of \( c \) and the stability of phases.

From this mechanical analogy it also follows that there exists exactly one value of \( c \) which satisfies the conditions on plus and minus infinity.

Fisher equation despite its visible simplicity has a number of peculiar features which are not typical to other RDE systems. In fact, since it has only one stable state, there is no question as to in which direction the population wave propagates. In real multistable systems, there is always a question of relative phase stability. Indeed, in analogy with physics, the areas of space corresponding to spatially homogeneous solutions of RDE are commonly termed phases. Continuing the analogy it becomes clear that traveling waves which switch the medium from one state into another correspond to non-stationary interfaces. Interestingly, another analogy with physics helps to understand which phase is more stable and, thus, will eventually occupy the entire space.

Let us consider a generic bistable system described by a single RDE. In this case, the nonlinear function \( f(u) \) is represented by a cubic form as shown on the figure. In the generic case, there will be three stationary points corresponding to the roots of \( f(u) = 0 \), where \( u_1 \) and \( u_3 \) are stable, while \( u_2 \) is unstable. If we now apply the usual trick with substituting the variables by \( z = x - ct \), we will find an equation which can be easily represented in the form analogous to the Newton equation of a particle with mass \( D \) moving along the gradient of a potential \( I(U) \) with friction \( c \). Let us consider in detail this potential function as it explains many properties of the original equation. Indeed \( U_1 \) and \( U_3 \) will correspond to the two maxima of potential while \( U_2 \) to the minimum. From the boundary conditions it follows that the particle starts on minus infinity on the top of one maximum and arrives at plus infinity into another with the zero speed. From this analogy it follows firstly that the difference of potentials \( I(U_1) - I(U_3) \) defines the direction of the motion. In the case exemplified by a figure, \( U_3 \) corresponds to a higher potential than \( U_1 \) and thus \( U_3 \) will be the stable, dominant phase. Secondly, it is intuitively clear that there is only one value of friction \( c \) such that friction losses along the way exactly equal to the difference of potentials. Therefore, there is only one value of wave speed \( c \) which corresponds to a traveling wave solution. This uniqueness of \( c \) eventually results in a unique solution \( U(x - ct) \) which satisfies the original equation. This means that both the velocity and the shape of the moving interface are completely defined by the properties of the medium (distributed system) and are independent of the initial conditions.
Critical size of the nucleus of the stable phase

It takes a nucleus of the stable phase larger than some critical size (red line) to achieve transition of the entire medium from metastable ($u_1$) to stable ($u_3$) phase.

The profile of a critical nucleus is an unstable solution of:

$$D \frac{d^2 u}{dx^2} + f(u) = 0$$

With boundary conditions:

$$\left. \frac{du}{dx} \right|_{x=0} = 0, \quad u \rightarrow u_i [x] \rightarrow \infty$$

We can find the value $u^*$ - the height of a critical nucleus without solving the equation:

Multiplying by $du/dx$ and integrating from 0 to infinity gives:

$$\int_0^\infty \left[ D \frac{du}{dx} \frac{d^2 u}{dx^2} + f(u) \frac{du}{dx} \right] dx = 0$$

Since first integral with boundary conditions equals to 0 we eventually get:

$$\int_{u_i}^{u^*} f(u) du = I(u^*) - I(u_i) = 0$$

So far we've been very vague regarding the initial conditions that develop into a stable wave propagating in the medium. Indeed, what does it take to induce a wave? Obviously, if the (infinite) medium is populated by a stable phase ($u_3$), any initial conditions there $u$ not equal $u_3$ on a finite interval will relax back to the stable phase. The converse is not true however. If the medium is initially populated by a metastable phase $u_1$, it takes initial conditions of special shape for the stable phase nucleus to survive inside the metastable phase. Here we can resort to our intuitive description of a medium as an array of diffusively coupled homogeneous boxes. It is clear that if in the initial profile $u(x)$ is less than the value of the saddle point $u_2$, in every box local reaction will try to return to the locally stable level $u_1$ and therefore any such initial profile will relax to $u(x)=u_1$ at every point $x$. Things are lot more complicated then on the part of the initial profile $u>u_2$ and everywhere else $u<u_2$. Then in those boxes where $u>u_2$, the dynamics will attempt to relax to $u_3$ while in those where $u<u_2$ to $u_1$. If we add now the diffusion coupling between the boxes, it will become clear that due to the tendency of the local dynamics the initial profile will shrink in width while growing taller. In fact, there will be exactly one such initial profile that does not either shrink or expand. This stationary solution is absolutely unstable as any perturbation will result in the growth or collapse. The profile in question is called a critical nucleus of the stable phase and is formally a solution of a stationary variant of RDE. There is a trick which allows to find the height of the nucleus without solving the equation which involves multiplying the equation by $du/dx$ and integrating it from 0 to plus infinity. Since the derivative is 0 both at 0 and at infinity, the first integral is also 0 and we obtain interesting equation for the integral $I$ of the function $f(u)$. If $f(u)$ is easily integrable function of $u$ (e.g., cubic polynomial) we can easily find the value of $u^*$.

Thus we see that there is a clear parallel between physical phase transitions of the 1st order and the transition of nonlinear reactive medium from one phase to another. Both require a nucleus exceeding critical size and occur via propagation of an interface that eventually expunges the metastable phase.
What to take home

- Biological systems are inherently spatially heterogeneous systems and the dependence on spatial variables needs to be explicitly included into the modeling.

- Random thermally-induced spatial motion of chemical molecules is described by the process of *diffusion*. The average distance $L_{	ext{diff}}$, the molecule travels is proportional to the square root of the product of travel time and the diffusion coefficient.

- Once the characteristic size of the system $L$ significantly exceeds the $L_{	ext{diff}}$, the ODEs describing the dynamics of the system should be replaced by *RDEs* – partial differential equations.

- Although intuitive understanding of spatially distributed system often helps, there is no direct equivalent between dynamics of RDE and the adjoining ODE.

- The simplest spatially distributed RDE system is the one whose adjoining ODE has *multistability*. The spatio-temporal patterns in such systems are *waves* of front type which serve as interfaces between the *phases* of the system.

- Multistable nonlinear distributed systems are analogous to physical systems with 1st order phase transitions. In fact, propagation of switch-type fronts is often called *nonlinear phase transitions*. 