Cellular Systems Biology and Biological Network Analysis

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Preface

Cells are systems. Standard engineering and mathematics texts should provide an excellent introduction to understanding how cells behave, mapping inputs to outputs. Unfortunately, cells are not linear, time-independent systems. Saturation and cooperative response break linearity. Cellular states change with time. Cells are not even deterministic, violating the assumptions of non-linear systems analysis.

This book provides a self-contained introduction to cells as non-linear, time-dependent, stochastic, spatial systems. Each major section is motivated by a canonical biological pathway or phenomenon that requires the introduction of new concepts. All the required mathematical techniques are developed from the motivating examples.

The book is designed as a text for advanced undergraduate or graduate students. Prerequisites are univariate calculus, linear algebra, basic molecular biology, and rudimentary facility with a programming language for computational experiments. Linear systems and Laplace transforms are helpful, but are also reviewed in the initial chapters. Each chapter is designed to be covered in an hour lecture, and problems are provided in an Appendix.

This book is developed from course notes for "Systems Bioengineering III: Genes to Cells," taught by me since 2007 as a required course for our B.S. in Biomedical Engineering.

Joel S. Bader, Baltimore, MD

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We left off last time with a model for a two-state biological signaling element,

$$(d/dt)x(t) = \beta(t) - \alpha x(t).$$

Here, $x(t)$ represents the concentration of the active form of a signaling molecule, usually meaning it is phosphorylated. The input is $\beta(t)$, and we consider it to be under our control. The rate that the activate form reverts to the inactive form is α.

Formally, we could write the solution as

$$[(d/dt) + \alpha]x(t) = \beta(t);$$

$$x(t) = [(d/dt) + \alpha]^{-1}\beta(t).$$

The problem is that we don't know what it means to take the inverse of an operator like the time derivative operator d/dt.

This is a lot like solving a matrix equation,

$$\mathbf{Ax} = \mathbf{b} - \alpha\mathbf{x}.$$

I use capital bold letters to indicate matrices and lower case bold to indicate column vectors. Elements of matrices and vectors are not bold, A_{ij} and x_i, We think about discretizing time so instead of $x(t)$ we have a vector $\mathbf{x}$ with elements $x_n = x(n\Delta t)$.

If we want this to be our actual problem, then $\mathbf{A}$ should be the time derivative operator in discrete form. Just to show you how we can do this, use the symmetric form

$$(d/dt)x_n = [x_{n+1} - x_{n-1}]/2\Delta t.$$

We also know that

$$(d/dt)x_n = \sum_{n'} A_{nn'}x_n = A_{n,n+1}x_{n+1} - A_{n,n-1}x_{n-1}.$$

$$A_{n,n'} = (1/2\Delta t)(\delta_{n',n+1} - \delta_{n',n-1}).$$

The discrete or Kronecker δ-function is 1 if its arguments are the same and 0 otherwise. One way to picture $\mathbf{A}$ is a tridiagonal matrix with 1's in the diagonal above the main diagonal, 0's in the main diagonal, and -1's in the diagonal below the main diagonal.

Formally, we could solve the algebraic equation as

$$\mathbf{x} = [\mathbf{A} + \alpha \mathbf{I}]^{-1}\mathbf{x}.$$

The matrix $\mathbf{I}$ is the identity matrix, with $I_{nn'} = \delta_{nn'}$ using our friend the δ-function. We wouldn't want to solve this by hand though because taking an inverse of a large matrix is difficult.

Instead this is why we learned about eigenvectors and eigenvalues because they change the matrix inverse into a scalar inverse. We're going to do exactly the same thing here by thinking about eigenfunctions and eigenvalues.

An operator A operates on a function $f(t)$ to give a new function $Af(t) = g(t)$. We will limit ourselves to operators that we could express as matrices if we made time discrete. The main operator we will consider is the time derivative operator d/dt. We will simplify our problem is we can express everything in terms of eigenfunctions of d/dt, functions for which

$$(d/dt)f(t) \propto f(t).$$

The proportionality constant could be any scalar. Pure exponentials are eigenfunctions of d/dt,

$$(d/dt)e^{\lambda t} = \lambda e^{\lambda t}.$$

We use λ because everyone knows that λ is the name of a generic eigenvalue. Just the same way that a matrix can have many different eigenvectors, each with a different eigenvalue, an operator can have many eigenfunctions. Here we have an infinite number.

We could index each eigenfunction by its eigenvalue, $f_\lambda(t) = e^{\lambda t}$. If λ is pure real, then we have functions that grow or decay with time. We'll start instead with eigenvalues that are pure imaginary, $\lambda = i\omega$, because Fourier transforms seem more symmetric than Laplace transforms. Our convention is to think about basis functions $\phi_\omega(t) = e^{i\omega t}$.

Now really we could have any scalar in front of $\phi_\omega t$ and it would still have the same eigenvalue $i\omega$. This is the same as with eigenvectors where we fix the overall scale by insisting that eigenvectors are normalized to have a dot product of 1. Actually we want their dot products to be orthonormal. For functions, rather than the dot product, we use the inner product,

$$\langle f(t)|g(t)\rangle \equiv \int_{-\infty}^{\infty} dt\, [f(t)]^* g(t),$$

where $[f(t)]^*$ is the complex conjugate of $f(t)$. For eigenfunctions of d/dt we could abbreviate the inner product as $\langle \omega' | \omega \rangle$. If we are thinking about discrete time, then the ω values are also discrete, and we want $\langle \omega' | \omega \rangle = \delta_{\omega',\omega}$. We will do this as a homework problem to see that the correct scalar for $\phi_\omega(t)$ is $1/\sqrt{2\pi}$, so that

$$\phi_\omega(t) = (1/\sqrt{2\pi})e^{i\omega t}.$$

Notice that the inner product has two factors of $1/\sqrt{2\pi}$, and

$$\langle\omega'|\omega\rangle = (1/2\pi)\int_{-\infty}^{\infty} dt\, e^{-i\omega' t} e^{i\omega t}.$$

Math tends to split these factors symmetrically between $\langle\omega|$ and $|\omega\rangle$. Enygineering and physics usually puts the entire factor of $1/2\pi$ into $|\omega\rangle$ so that

$$x(t) = \int_{-\infty}^{\infty} d\omega \hat{x}(\omega)|\omega\rangle = \int_{-\infty}^{\infty} (d\omega/2\pi)\hat{x}(\omega)e^{i\omega t}$$

$$\hat{x}(\omega) = \langle\omega|x\rangle = \int_{-\infty}^{\infty} dt e^{-i\omega t} x(t).$$

While this would be the discrete Kronecker δ-function for a discrete time representation, in the limit that we have continuous time it becomes the Dirac δ-function, $\delta(\omega-\omega')$. For any finite value of $\Delta\omega = \omega - \omega'$, the integral goes to 0. Actually the convergence of the integral to 0 is tricky, but you can think about the indefinite integral being $e^{i\Delta\omega t}/i\Delta\omega$, which is evaluated at endpoints T and $-T$. These are so big that $e^{i\Delta\omega T}$ is oscillating so rapidly that it looks like 0.

When $\Delta\omega \to 0$, the function $\delta(\Delta\omega) \to \infty$, but in a very nice way: the area under the δ-function is 1. For any finite ε,

$$\int_{\omega-\varepsilon}^{\omega+\varepsilon} d\omega' \delta(\omega'-\omega) = 1.$$

This also makes integrals involving the δ-function easy,

$$\int_{-\infty}^{\infty} d\omega' f(\omega')\delta(\omega'-\omega) = f(\omega).$$

It just picks out the value of the rest of the integrand when its argument is 0.

If this doesn't make sense, don't worry. You'll prove all of this in homework.

As a note, we'll do one more quick thing with inner products. First notice that $\sum_{\omega'} |\omega'\rangle\langle\omega'|$ behaves like the identity matrix for functions. For example, if $f(t)$ can be expressed as $\sum_{\omega} \hat{f}(\omega)|\omega\rangle$, then

$$\sum_{\omega'} |\omega'\rangle\langle\omega'|f\rangle = \sum_{\omega'}\sum_{\omega} |\omega'\rangle\langle\omega'|\hat{f}(\omega)|\omega\rangle.$$

Remember that $\hat{f}(\omega)$ is just a scalar expansion coefficient that we can more around to get the inner product $\langle\omega'|\omega\rangle$,

$$\sum_{\omega'} |\omega'\rangle\langle\omega'|f\rangle = \sum_{\omega'}\sum_{\omega} \hat{f}(\omega)|\omega'\rangle\langle\omega'|\omega\rangle = \sum_{\omega'}\sum_{\omega} \hat{f}(\omega)|\omega'\rangle\delta_{\omega',\omega}.$$

The δ-function means that one of the sums goes away, finally giving

$$\sum_{\omega'} |\omega'\rangle\langle\omega'|f\rangle = \sum_{\omega} \hat{f}(\omega)|\omega\rangle = f(t).$$

Since this is true for any function $f(t)$ that can be expressed in the basis of $|\omega\rangle$, we conclude that $\sum_\omega |\omega\rangle\langle\omega|$ can be used as an identify operator for functions.

We can use this property to calculate the inner product $\langle f|g\rangle$ for two functions $f(t)$ and $g(t)$ as

$$\langle f|g\rangle = \langle f|\big[\sum_\omega |\omega\rangle\langle\omega|\big]|g\rangle = \sum_\omega \langle f|\omega\rangle\langle\omega|g\rangle.$$

The inner product $\langle\omega|g\rangle = \hat{g}(\omega)$. The inner product $\langle f|\omega\rangle$ is the complex conjugate of $\langle\omega|f\rangle = \hat{f}(\omega)$. Therefore, $\langle f|\omega\rangle = \hat{f}^*(\omega)$. This means that

$$\langle f|g\rangle = \sum_\omega \hat{f}^*(\omega)\hat{g}(\omega).$$

If $f(t)$ is pure real, then $\hat{f}^*(\omega) = \hat{f}(-\omega)$, and

$$\langle f|g\rangle = \sum_\omega \hat{f}(-\omega)\hat{g}(\omega).$$

Returning to our problem, our plan is to write each of our time domain functions as a sum of eigenfunctions.

$$x(t) = \sum_\omega \hat{x}(\omega)|\omega\rangle.$$

$$\beta(t) = \sum_\omega \hat{\beta}(\omega)|\omega\rangle.$$

The terms $\hat{x}$ and $\hat{\beta}$ are just the expansion coefficients. Putting this expansion into the starting equation,

$$(d/dt)\sum_\omega \hat{x}(\omega)|\omega\rangle = \sum_\omega \hat{\beta}|\omega\rangle > -\alpha\sum_\omega \hat{x}(\omega)|\omega\rangle.$$

Now we can eliminate the time derivative in favor of the eigenvalue,

$$\sum_\omega (i\omega+\alpha)\hat{x}(\omega)|\omega\rangle = \sum_\omega \hat{\beta}(\omega)|\omega\rangle.$$

Remember that what we know is $\beta(t)$, which means that we should be able to figure out the expansion coefficients $\hat{\beta}(\omega)$. We want to solve for the output expansion coefficients $\hat{x}(\omega)$. We can do this for a particular value ω' by taking the inner product,

$$\sum_\omega (i\omega+\alpha)\hat{x}(\omega)\langle\omega'|\omega\rangle = \sum_\omega \hat{\beta}(\omega)\langle\omega'|\omega\rangle.$$

$$(i\omega'+\alpha)\hat{x}(\omega') = \hat{\beta}(\omega').$$

$$\hat{x}(\omega) = (i\omega+\alpha)^{-1}\hat{\beta}(\omega).$$

We can write down the formal solution,

$$x(t) = \sum_\omega \hat{x}(\omega)|\omega\rangle.$$

For continuous time, the sum becomes an integral, with details in the homework,

$$x(t) = (1/2\pi)\int_{-\infty}^{\infty} d\omega (i\omega + \alpha)^{-1} e^{i\omega t}\hat{\beta}(\omega).$$

Substituting the inner product that gives us the expansion coefficient $\hat{\beta}(\omega)$,

$$x(t) = (1/2\pi)\int_{-\infty}^{\infty} d\omega (i\omega + \alpha)^{-1} e^{i\omega t}\int_{-\infty}^{\infty} dt' e^{-i\omega t'}\beta(t')$$

We will next change the order of the integrals. We can usually do this for physical systems. We will always be able to do it in this class.

$$x(t) = \int_{-\infty}^{\infty} dt' \frac{1}{2\pi}\int_{-\infty}^{\infty} d\omega \frac{\exp[i\omega(t-t')]}{i\omega + \alpha}\beta(t').$$

Let's think of this as a convolution or a filter,

$$x(t) = \int_{-\infty}^{\infty} dt' H(t-t')\beta(t'),$$

where the response function is

$$H(t-t') = \frac{1}{2\pi}\int_{-\infty}^{\infty} d\omega \frac{\exp[i\omega(t-t')]}{i\omega + \alpha}.$$

Take a step back and breathe after the math blizzard. We have an output $x(t)$ that comes from an ODE model for a system that is driven by input $\beta(t)$. In a causal universe, $x(t)$ should only depend on the input at times before t,

$$x(t) = \int_{-\infty}^{t} dt' H(t-t')\beta(t').$$

Plot twist! Our integral doesn't stop at t. The integral goes to infinity. What are the possibilities?

1. We made a math mistake somewhere.
2. The universe (or our model for it) is not causal.
3. There is something special about the response function $H(t)$ for causal systems.

Spoiler alert: it's the last one. Response functions for classical causal systems are only non-zero for responses to inputs in the past. In other words, if the response function $H(t-t')$ is the response of the system at time t to an input at time t', then $H(t-t')$ must be 0 for $t < t'$. Next class we'll show this by doing the integral for our system's response function.

Chapter 3

The Laplace Transform and Complex Variables

We left ourselves with the puzzle of the response function,

$$H(t) = (1/2\pi)\int_{-\infty}^{\infty} d\omega\, \frac{e^{i\omega t}}{i\omega + \alpha}.$$

We'll factor the i from the denominator,

$$H(t) = \frac{1}{2\pi i}\int_{-\infty}^{\infty} d\omega\, \frac{e^{i\omega t}}{\omega - i\alpha}.$$

Much of math depends on multiplying by 1 in an interesting way (as we did previously using $1 = \sum_\omega |\omega\rangle\langle\omega|$) or by adding 0 in an interesting way. Here well add 0 to the integral in a way that changes the integration from a line integral to an integral over a closed contour.

We start by thinking about ω in the complex plane. We can write $\omega = u + iv$, where u and v are pure real, $u = \Re(\omega)$ is the real part of ω, and $v = \Im(\omega)$ is the imaginary part of ω. The exponential factor in the integrand is $e^{i\omega t} = e^{i(u+iv)t} = e^{iut}e^{-vt}$. The line integral to evaluate is

$$H(t) = \lim_{U\to\infty}(2\pi i)^{-1}\int_{-U}^{U} du \frac{e^{iut}e^{-vt}}{u + i(v-\alpha)}.$$

At the end of the line at U, for $t > 0$, we'll take a left turn. Call this integral $A/2\pi i$,

$$A = \lim_{V\to\infty}\int_0^V dv \frac{e^{iUt}e^{-vt}}{U + i(v-\alpha)}.$$

We care about the magnitude of A,

$$|A| = |\lim_{V\to\infty}\int_0^V dv \frac{e^{iUt}e^{-vt}}{U + i(v-\alpha)}| \leq \int_0^V dv \frac{|e^{iUt}e^{-vt}|}{|U + i(v-\alpha)|},$$

since a very reasonable theorem tells us that the absolute value of an integral is no larger than the integral of the absolute value of the integrand. Next, since $|U+i(v\alpha)| \le |U|$, and $|e^{iUt}| = 1$,

$$|A| \le \lim_{V\to\infty} \int_0^V dv \frac{e^{-vt}}{|U+i(v-\alpha)|} \le (1/U) \int_0^V dv e^{-vt}$$

Finally we have an integral we can do!

$$|A| \le 1/Ut.$$

Remember that we are taking the limit $U \to t$. For any finite t, $1/Ut \to 0$, which means that $A = 0$.

Now we turn left again and call this line integral $B/2\pi i$, with magnitude

$$|B| = |\lim_{U,V\to\infty} \int_U^{-U} du \frac{e^{iut}e^{-Vt}}{u+i(V-\alpha)}|.$$

Here we add the absolute value inside the integral,

$$|B| \le |\lim_{U,V\to\infty} \int_U^{-U} du \frac{|e^{iut}e^{-Vt}|}{|u+i(V-\alpha)|}| \le \frac{e^{-Vt}}{V} |\int_U^{-U} du 1|.$$

This is another integral that is easy,

$$|B| \le \lim_{U,V\to\infty} e^{-Vt}(2U/V).$$

If U and V approach ∞ together, then $2U/V \to 2$, and $|B| \le 2e^{-Vt}$. For finite t, $\lim_{V\to\infty} 2e^{-Vt} = 0$, and $|B| = 0$.

We take another left turn to close the circuit, adding on $C/2\pi i$, with

$$C = \int_V^0 dv \frac{e^{-iUt}e^{-vt}}{-U+i(v-\alpha)}.$$

Notice that $C = A^*$, so $C = 0$ as well. This means that

$$H(t) = H(t) + (A+B+C)/(2\pi i) = (1/2\pi i) \oint e^{i\omega t}/(\omega - i\alpha),$$

where the $\oint$ means that the integral is over a closed contour. The contour we are considering is the large loop across the real axis, then counterclockwise into the upper imaginary plane and back down and around.

We will stop for another puzzler. Suppose that we have a function $F(\omega)$ with derivative $(d/d\omega)F(\omega) = f(\omega)$. We do an integral over a closed loop, starting at some value ω_0 and ending at the same point. Over that loop, we want to evaluate the integral $\oint d\omega f(\omega)$. In general, it should be true that

$$\int_{\omega_0}^{\omega_1} d\omega f(\omega) = F(\omega)|_{\omega_0}^{\omega_1} = F(\omega_1) - F(\omega_0).$$

For the closed loop, then, should we get $F(\omega_0) - F(\omega_0) = 0$?

The error we've made is that the endpoint isn't ω_0. Instead, if we write ω_0 in terms of a magnitude $|\omega_0|$ and a phase ϕ, $\omega_0 = |\omega_0|e^{i\phi}$, our ending point has accumulated a phase of 2π, $\omega_1 = |\omega_0|e^{i(\phi+2\pi)}$. For some functions, $F(\omega_0) = F(\omega_1)$. For these functions, the contour integral is 0. For many functions, though, $F(\omega_0) \neq F(\omega_1)$, and the contour integral has a non-zero value. For example, think about $F(\omega) = \omega^{1/2}$, and for simplicity choose $\omega_0 = 1$. In this case, $F(\omega_1) = (e^{2\pi i})^{1/2} = e^{\pi i} = -1$, $F(\omega_0) = 1$, and the contour integral gives -2.

What type of function $F(\omega)$ contributes nothing to the contour integral? Suppose that $F(\omega) = \omega^n$ where n is any integer. Then $F(\omega_1) = |\omega_0|^n e^{n(\phi i+2\pi i} = |\omega_0|^n e^{n\phi i} e^{2n\pi i} = F(\omega_0)$. A function that can be expressed as a sum of positive or negative integer powers never contributes to a contour integral. Fractional powers can contribute, though, because when n is not an integer, $e^{2n\pi i} \neq 1$.

A very special type of function $F(\omega)$ that can contribute is $F(\omega) = \ln(\omega)$ because $\Im \ln(\omega)$ is equal to the phase. For this function around a contour starting at $\omega_0 = |\omega_0|e^{i\phi}$ and ending at $\omega_1 = \omega_0 e^{2\pi i}$,

$$F(\omega_1) - F(\omega_0) = \ln(|\omega_0|) + 2\pi i + \phi i - \ln(|\omega_0|) - \phi i = 2\pi i.$$

Remember that $F(\omega)$ is integral. The integrand in the contour integral is $f(\omega) = (d/d\omega)F(\omega)$. For $F(\omega) = \ln(\omega)$, $f(\omega) = 1/\omega$. And the contour integral for $H(t)$ has something like $1/\omega$ in the denominator.

Returning to the contour integral for $H(t)$,

$$H(t) = (1/2\pi i) \oint d\omega e^{i\omega t}/(\omega - i\alpha).$$

To make things simpler, change variables to $z = \omega - i\alpha$, with

$$H(t) = \frac{e^{-\alpha t}}{2\pi i} \oint dz e^{zt}/z.$$

Then we do a power series expansion about this point. If we think about the contour for ω starting at 0 then making a big counterclockwise loop, then the contour for z starts at $z_0 = -i\alpha$ and ends at $z_1 = z_0 e^{2\pi i}$.

We can do a series expansion of $e^{zt} = \sum_{n=0}^{\infty} (zt)^n/n!$ and integrate term by term,

$$H(t) = \frac{e^{-\alpha t}}{2\pi i} \oint dz(1/z) \sum_{n=0}^{\infty} z^n t^n/n! = \frac{e^{-\alpha t}}{2\pi i} \sum_{n=0}^{\infty} (t^n/n!) \oint dz z^{n-1}.$$

From our work before, we know that all the integer terms give 0 except for the term with $n = 0$, integrating $1/z$, which gives a factor of $2\pi i$. The factor $t^0/0! = 1$. Therefore the response function for $t > 0$ is

$$H(t) = e^{-\alpha t}.$$

What about for $t < 0$? In this case, we follow the same logic of adding 0 to the integral, but instead of closing in the upper half plane we have to close in the lower half plane to make $e^{i\omega t}$

small. We end up with a clockwise rather than counterclockwise integral,

$$H(t) = (1/2\pi i)\oint d\omega e^{-i\omega|t|}/(\omega - i\alpha) = (1/2\pi i)\oint d\omega.$$

We can think about a power series expansion again. For any value of ω in the lower half plane, write $\omega_0 = \omega - i\alpha$, and consider nearby points $\omega + z$. For these points,

$$1/(\omega + z - i\alpha) = 1/(\omega_0 + z) = 1 - (z/\omega_0) + (z/\omega_0)^2 - (z/\omega_0)^3 + \dots,$$

which is a convergent series when $|\omega_0| > 0$. The smallest magnitude of ω_0 is for $\omega = 0$, $|\omega_0| = \alpha$. Provided that $\alpha > 0$, we have a convergent series everywhere in the lower half plane, and all the powers of z are positive integers. There is no contribution to the contour integral, and $H(t) = 0$ for $t < 0$.

For Laplace transforms, instead of $\lambda = i\omega$, we use $\lambda = s$ for the eigenvalue. In other words, $s = i\omega$, or $\omega = -is$. The forward transforms are

$$\mathscr{F}[f(t)] = \hat{f}(\omega) = \int_{-\infty}^{\infty} dt e^{-i\omega t} f(t)$$

$$\mathscr{L}[f(t)] = \tilde{f}(s) = \int_{-\infty}^{\infty} dt e^{-st} f(t).$$

The inverse transforms are

$$f(t) = (1/2\pi)\int_{-\infty}^{\infty} d\omega\, e^{i\omega t}\hat{f}(\omega)$$

$$f(t) = (1/2\pi i)\int_{-i\infty}^{i\infty} ds\, e^{st}\tilde{f}(s) = (1/2\pi i)\oint ds\, e^{st}\tilde{f}(s).$$

For the inverse Laplace transform for positive time, we close the contour in the left half-plane. For positive time, we close the contour in the right half-plane.

Nothing in the definition of the Laplace transform requires that we start the time integral at 0. For an initial value problem, we essentially are saying that $f(t) = 0$ for $t < 0$ and then start the integral at 0.

If we think of a Laplace space eigenfunction of d/dt as a normalized version of e^{st}, then the eigenvalue is s. This means that there is a correspondence between d/dt in the time domain and s in the Laplace domain. We will look at two examples.

First, consider time displacement, $f(t+a)$. A Taylor series for $f(t+a)$ around $f(t)$ is

$$f(t+a) = f(t) + a(d/dt)f(t) + (a^2/2)(d/dt)^2 f(t) + (a^3/3!)(d/dt)^3 f(t) + \dots = \sum_{n=0}^{\infty}(a^n/n!)(d/dt)^n f(t).$$

If d/dt were a scalar, we could write the sum as an exponential,

$$\sum_{n=0}^{\infty}(a^n/n!)(d/dt)^n = \exp[a(d/dt)].$$

We can do the same for operators if we just say to ourselves that the series expansion defines the meaning of the exponential. Therefore we find that

$$f(t+a) = e^{a(d/dt)} f(t).$$

For the Laplace transform,

$$\mathscr{L}[f(t+a)] = \int_{-\infty}^{\infty} dt\, e^{-st} f(t+a).$$

Changing variables to $u = t + a$, $st = su - sa$,

$$\mathscr{L}[f(t+a)] = \int_{-\infty}^{\infty} dt\, e^{-su+sa} f(u) = e^{as} \tilde{f}(s).$$

To summarize, $f(t+a) = e^{a(d/dt)} f(t)$ and $\mathscr{L}[f(t+a)] = e^{as}\mathscr{L}[f(t)]$.

We similarly look at $\mathscr{L}[(d/dt)f(t)]$. Here we consider an initial value problem where $f(t) = 0$ for $t < 0$, and then we change $f(t)$ to $f(0)$ at $t = 0$. This is done by integrating by parts,

$$\mathscr{L}[(d/dt)f(t)] = \int_0^{\infty} dt e^{-st} (d/dt) f(t) = e^{-st} f(t)|_0^{\infty} + s\int_0^{\infty} dt\, e^{-st} f(t) = -f(0) + s\tilde{f}(s).$$

Again, the (d/dt) in the time domain becomes a factor of s in the Laplace domain.

An important property of the Laplace transform is the convolution theorem. The convolution $f \star g(t)$ is defined as

$$f \star g(t) = \int^t dt' f(t-t') g(t').$$

Usually we are interested in initial value problems where $f(t) = g(t) = 0$ for $t = 0$ and the system turns on at $t = 0$, in which case the starting point of the integral is $t = 0$. Note that for a linear system with response function $H(t)$, the response $x(t)$ to an input $\beta(t)$ is $x(t) = H \star \beta(t)$.

The Laplace transform of a convolution is

$$\mathscr{L}[f \star g(t)] = \int_0^{\infty} dt\, e^{-st} \int_0^t dt'\, f(t-t') g(t').$$

Changing variables from t and t' to $t - t'$ and t' and multiplying by $1 = e^{st'} e^{-st'}$,

$$\mathscr{L}[f \star g(t)] = \int_0^{\infty} dt' e^{-st'} g(t') \int_0^{\infty} d(t-t')\, e^{-s(t-t')} f(t-t') = \tilde{f}(s)\tilde{g}(s).$$

For a linear system, the response in Laplace space is $\tilde{x}(s) = \tilde{H}(s)\tilde{\beta}(s)$.

Now a few notes on the inverse Laplace transform. Suppose we are working on an initial value problem with step input, $\beta(t) = \beta_0$ for $t > 0$ and $\beta(t) = 0$ for $t < 0$. The Laplace transform is

$$\tilde{\beta}(s) = \int_0^{\infty} e^{-st} \beta_0 = \beta_0 / s.$$

When we go to do the inverse transform, though, we notice that the pole at $s = 0$ lies on the integration contour. What do we do? The answer depends on the physical interpretation of the problem. Here, our convention is that everything dies. We don't allow an input that stays on forever. Instead, we take an input of the form $\beta(t) = \beta_0 e^{-\varepsilon t}$ and take the limit $\varepsilon \to 0$. For this input,

$$\tilde{\beta}(s) = \beta_0/(s+\varepsilon),$$

and the pole is inside the integration contour. Therefore for $t > 0$ when we close the contour on the left, we get the full value of the pole, $\beta(t) = \beta_0$. For $t < 0$, we close the contour on the right, there are no poles, and $\beta(t) = 0$. Some texts will tell you to "shift the contour to the right of the imaginary axis" or "shift the contour to the right of any poles", but really you have to know how the equations correspond to the physical system to be sure about what to do. And you also have to know that for negative t you close on the right.

Anywhere that a function is well behaved, you can move an integration contour without affective the result. This means that for a function with multiple poles, you can evaluate their contributions separately,

$$(1/2\pi i) \oint e^{st}/(s+\alpha)(s+\beta) = e^{-\alpha t}/(-\alpha+\beta) + e^{-\beta t}/(-\beta+\alpha).$$

For a second-order pole $1/(s+\alpha)^2$, you can take the limit as $\beta \to \alpha$. More generally, for

$$(1/2\pi i) \oint f(s)/(s+\alpha)^n$$

where $f(s)$ is well behaved for s close to $s = -\alpha$, the solution is to do a series expansion of $f(s)$ around this point. The only term that contributes is $[1/(n-1)!](d/ds)^{n-1} f(s)|_{-\alpha}$.

And that is it for the theory of Laplace transforms.

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Appendix A

Problems