June Bugs in the Swimmin’ Pool

An Analogy for the Concept of Clearance

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As shown in the above figure, we are beginning with the following assumptions: 1) pool capacity is 15,000 gals and the pump filtering the pool water pumps 30 gal/min. Every june bug that enters the skimmer is filtered out, and the water is immediately recycled back to the pool.

If no new june bugs landed in the pool, the remaining june bugs would be constantly “diluted” by this water from which the june bugs had been removed. It can be shown mathematically that a constant fraction of the pool is being “cleared” of june bugs per minute, namely 30 gallons of the total gallons in the pool each minute. After a certain period of time half of the bugs will be gone ($t_{1/2}$, the half-time). In another half-time, half of what had remained will be gone and so on. That is, at $t=0$, bugs = 100% of starting amount; at $t= 1 \times t_{1/2}$, bugs = 50% of starting amount; at $t= 2 \times t_{1/2}$, bugs = 25% of starting amount, and so on. Irrespective of whether a half-time is referring to seconds, minutes, hours, or days, 97% of the bugs will be gone after 5 half-times. This is called first-order clearance, and is the manner in which our body gets rid of most pharmaceutical agents.

As long as these “first order” kinetics apply, 97% of X is eliminated in 5 $t_{1/2}$
However, now back to the real world... the problem with june bugs is that they keep proliferating and flying into the pool. Let's assume they do this at a constant rate, say one per minute. And let's say they started flying into the pool on June 1. Let's also ignore the fact that they float and state that they are thoroughly mixed with all 15,000 gals of pool water.

- What are the odds that the first bug to land in the pool is filtered out in the first minute? Not very good... 30 gals filtered per min /15,000 gals = 1 in 500. So, that bug will probably stay for awhile.
- A minute later, another june bug plops into the pool, so there is now 1 bug per 7,500 gallons of water. The odds of getting rid of one of them are now 30/7500 = 1 in 250.
- Another bug lands, odds of getting rid of him are 1 in 125 and so on. However, at some point, we will start getting rid of june bugs. We will come into equilibrium.

Where will this point be? Where will input = output?? Because 30 gallons of the pool are being cleared per minute and 1 bug is landing in the pool per minute, there will be a net accumulation of bugs in the pool until there is one bug per 30 gallons. After that, your skimmer gets rid of -- on average-- exactly what is entering the pool... you've reached “equilibrium” at this concentration of bugs (i.e., 500 in the pool).

Now let's assume that your pool pump loses its efficiency. Instead of being able to pump 30 gallons per minute, it can now only pump 15 gallons per minute. Do the june bugs care? No! They keep piling into the pool at a rate of 1 per minute. Based on the above description, it should be obvious that there is going to be a net accumulation until there is 1 june bug per 15 gallons or ~1000 bugs in the pool at all times. The concentration of june bugs doubled because the “clearance rate” was cut in half (from 30 gal/min to 15 gal/min), but once again, the pool is in equilibrium... one bug is entering the pool per minute and 1 bug is being trapped and eliminated per minute.

So, do you see that clearance is a flow rate? It's the volume of water from which all of the june bugs (no matter how many were contained in it) is eliminated per minute. If the product of interest is a single dose of an exogenous product, a constant fraction of it will be eliminated per unit time until it is gone. However, if “X” is something that the body generates as waste or if “X” is a drug that is being administered at fixed intervals, the plasma level of “X” will center about the level at which the average minute production or intake per minute equals the average output per minute. If the clearance rate halves, the concentration doubles (1/2 clearance rate * 2 times concentration = 1 daily output); similarly 1/4 clearance rate * 4 times concentration = 1 daily output, 1/10 clearance rate * 10 times concentration = 1 daily output, and so on.

Creatinine is a waste product produced by the muscle mass of the body, something that doesn't change markedly from day to day. Consequently, creatinine is produced at a relatively constant rate and is continuously dumped into the extracellular space for elimination, similar to the june bugs above. Creatinine is freely filtered (i.e., small and dissolved in plasma) and is typically assumed to be neither secreted* nor reabsorbed. That is, if it is filtered, it ends up in the urine, which makes it a good endogenous marker for glomerular filtration rate.

- The clearance rate of the kidneys for any substance can be calculated by measuring the urine flow rate, the urine concentration of substance X and the plasma concentration of substance X as follows:

\[
C_X = \frac{U_X \times V}{P_X}
\]

where

- \(C_X\) = clearance of \(X\) (ml/min)
- \(U_X\) = urinary concentration of \(X\) (e.g., mg/ml)
- \(P_X\) = plasma concentration of \(X\) (e.g., mg/ml)
- \(V\) = urine flow rate (ml/min)
What is the possible range of clearances for solute x?

- Any substance that the kidney normally reabsorbs completely (e.g., glucose), will have a clearance rate of 0 ml/min.
- Any substance that is freely filtered and neither secreted nor reabsorbed will have a clearance rate equal to the glomerular filtration rate.
- However, this is not the upper limit because only a fraction of the plasma that enters the kidney (e.g., 20%) is actually filtered. So, how do we measure all of the plasma entering the kidney? For this calculation, we need something that is completely removed from the plasma that enters the kidney. Para-aminohippurate (PAH) meets these criteria by being filtered and secreted to the point of being completely eliminated from the plasma exiting the kidney in the renal vein. The clearance of PAH is a measure of effective renal plasma flow (RPF).
- Thus, the rate at which filtrate can be cleared of solute ranges from 0 to RPF.

In a clinical setting, 24 hr urine collections are not routinely obtained. However, if John Q. Public’s serum creatinine concentration was recently 1 mg/dL, and has now increased to 2 mg/dL, what do you know about his glomerular filtration rate?

Accurate blood flow measurement today is an invasive technique that requires placing a special probe around a blood vessel. Electromagnetic flow measurement apparatus first appeared on the market in the late 1970’s and doppler transit time flow measurement apparatus appeared in the late 1980’s. I find it rather amazing that long before blood flow could be measured with a machine, kidney scientists following the procedure established by Homer Smith (pictured) in ~ 1945 could calculate this value by simply infusing PAH intravenously and then measuring its rate of excretion in the urine, its plasma concentration and the hematocrit. Moreover, clearance calculations remain the only way of measuring glomerular filtration rate to this day. The most prestigious award in renal physiology is the Homer W. Smith Award.

*There are two errors in this measurement, but they tend to cancel one another out.

**This statement is a textbook approximation; ~ 10-15% of the plasma that enters the kidney flows into regions other than the nephrons (e.g., fat, connective tissue) and exits through the renal vein. To get a more accurate estimate of renal plasma flow, scientists often multiply the clearance value obtained from PAH, the effective RPF by 1.1. Dividing this value by (1- Hct) will give a value for RBF the coincides more closely with that measured using a flowmeter.