

LORENZ CURVES AND DRUG DISSOLUTION

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Abstract

Recent papers outline a useful semi-analytical technique for approximating the drug dissolution from a simple horizontally layered medicinal tablet (a compact) [1, 4]. Their solution is calculated for the specific cases of three- and five-layer compacts. An earlier technical note generalises their result for any number of layers and considers the behaviour of the solution as the number of layers becomes very large. This note concludes the consideration of the behaviour of the solution as the number of layers becomes very large. We observe that the underlying mathematics is essentially the same used to describe the distribution of wealth in a society, visualised as Lorenz curves.

1 Introduction

In a previous technical note [3], we considered the results presented by Crane et al. in the paper, A Pohlhausen Solution for the Mass Flux From a Multi-layered Compact in the USP Drug Dissolution Apparatus [1], or *the Pohlhausen paper*. This paper is concerned with approximating the mass transfer rate, \dot{m} , of *drug* and *excipient* from a simple horizontally layered tablet, or compact, in a USP paddle dissolution apparatus [5]. See Figure 1 and others, below. Excipients are medicinally inert materials used to bind

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Figure 1: The prototype multi-layer compact, or tablet, considered here: a 3-layer version is shown. The tablet can be imagined as a typical cylindrical over-the-counter *dosage form*, e.g. an (unusual) aspirin tablet.

or influence dissolution behaviour, among other things. This rather idealised prototype tablet configuration is a useful starting point for some aspects of the mathematical analysis of dissolution³.

In our previous note, we determined that we can quite easily generalise the special results of Crane et al. [1] to p evenly spaced layers, by writing,

$$\frac{\dot{m}_{\text{excipient}, p \text{ layers}}}{\dot{m}_{\text{excipient}, \text{ single layer}}} = \left[\sum_{n=0}^{p-1} \left(\frac{p-n}{p} \right)^{\frac{3}{4}} (-1)^n \right]^{\frac{2}{3}} \quad (1)$$

and

$$\frac{\dot{m}_{\text{drug}, p \text{ layers}}}{\dot{m}_{\text{drug}, \text{ single layer}}} = \left[1 - \sum_{n=0}^{p-1} \left(\frac{p-n}{p} \right)^i (-1)^n \right]^{\frac{2}{3}} \quad (2)$$

Where \dot{m} is the mass transfer rate of drug or excipient, as denoted, from the compact. We also observed that the drug release rates predicted by this generalised solution converge on a fixed value as the number of layers,

³For the interested reader, this was discussed in a little more detail in an earlier paper [4].

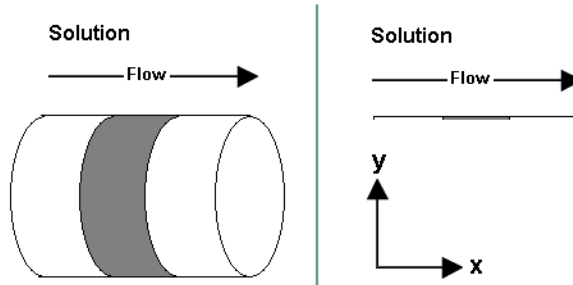


Figure 2: The multi-layer compact can be idealised as a one-dimensional object if the radius of the compact is sufficiently large compared to its length, i.e. for a stumpy cylinder. A 3-layer compact with one layer of drug is again shown; a compact with a larger number of layers can be readily imagined.

p , becomes very large. The question remains, can we prove that this will always be true?

To answer to this question, we must demonstrate that the following series converges to 0.5 for all indices $i > 0$ as p becomes very large, i.e.:

$$\sum_{n=0}^{p-1} \left(\frac{p-n}{p} \right)^i (-1)^n \rightarrow 0.5 \quad (3)$$

for all $i > 0$ as p becomes large.

2 Steps to a Solution

2.1 Numerical Demonstration

Using a simple Python script, we can easily show that, for indices, i , greater than 0, the sum of the series appears to converge towards 0.5 as p becomes large. This seems to be true for all $p > 1$, both odd and even. A simple version of the script is given as an appendix. A sample of the numerical results is reproduced in the table below.

$i :$	0.25	0.75	1.00	2.00	3.00	4.00
$p = 3$	0.8562	0.7009	0.6667	0.6667	0.7407	0.8148
$p = 5$	0.8078	0.6319	0.6000	0.6000	0.6480	0.6960
$p = 101$	0.6400	0.5118	0.5050	0.5050	0.5074	0.5099
$p = 1,001$	0.5786	0.5020	0.5005	0.5005	0.5007	0.5010
$p = 10,001$	0.5442	0.5003	0.5000	0.5000	0.5001	0.5001
$p = 100,001$	0.5248	0.5001	0.5000	0.5000	0.5000	0.5000
$p = 1,000,001$	0.5140	0.5000	0.5000	0.5000	0.5000	0.5000
$p = 10,000,001$	0.5079	0.5000	0.5000	0.5000	0.5000	0.5000
$p = 100,000,001$	0.5044	0.5000	0.5000	0.5000	0.5000	0.5000
$p = 1,000,000,001$	0.5025	0.5000	0.5000	0.5000	0.5000	0.5000

Table 1: Script output: as p becomes large, the sum of the series clearly tends to 0.5.

On the basis of the results of these numerical experiments, and without recourse to a rigorous mathematical treatment, it seems *likely* that the series converges to 0.5 for all indices $i > 0$ as p becomes very large.

2.2 Analytical Solution for an Index, $i = 2$

$$\sum_{n=0}^{p-1} \left(\frac{p-n}{p} \right)^2 (-1)^n = \frac{1}{p^2} [p^2 - (p-1)^2 + (p-2)^2 - (p-3)^2 + \dots]$$

Group in pairs, denoted as $2n$ and $2n-1$ where $n = 1, 2, 3, \dots, p/2$. Since $x^2 - y^2 = (x-y)(x+y)$, we can write,

$$\sum_{n=0}^{p-1} \left(\frac{p-n}{p} \right)^2 (-1)^n = \frac{1}{p^2} \sum_{n=1}^{\frac{p}{2}} ((2n - (2n-1)) \times (2n + (2n-1)))$$

But $2n - (2n-1) = 1$, so we can write,

$$\begin{aligned}
\sum_{n=0}^{p-1} \left(\frac{p-n}{p}\right)^2 (-1)^n &= \frac{1}{p^2} \sum_{n=1}^{\frac{p}{2}} 1 \times (2n + (2n-1)) \\
&= \frac{1}{p^2} \sum_{n=1}^{\frac{p}{2}} (4n-1) \\
&= \frac{1}{p^2} \left(4 \left[\frac{\frac{p}{2} \left(\frac{p}{2} + 1 \right)}{2} \right] - \frac{p}{2} \right)
\end{aligned}$$

Multiplying in by $\frac{1}{p^2}$, it is clear that $\left(\frac{1}{p^2}\right) \times \left(\frac{p}{2}\right) = \frac{1}{2p}$ tends to 0 as $p \rightarrow \infty$. Simplifying, we find that,

$$\sum_{n=0}^{p-1} \left(\frac{p-n}{p}\right)^2 (-1)^n \rightarrow \frac{1}{2} \text{ as } p \rightarrow \infty$$

2.3 Analytical Solution for an Index, $i = 3$

$$\sum_{n=0}^{p-1} \left(\frac{p-n}{p}\right)^3 (-1)^n = \frac{1}{p^3} [p^3 - (p-1)^3 + (p-2)^3 - (p-3)^3 + \dots]$$

Group in pairs, again denoted as $2n$ and $2n-1$ where $n = 1, 2, 3, \dots, p/2$. Since $x^3 - y^3 = (x-y)(x^2 + xy + y^2)$, we can write,

$$= \frac{1}{p^3} \sum_{n=0}^{\frac{p}{2}} (2n - (2n-1)) \times ((2n)^2 + 2n(2n-1) + (2n-1)^2)$$

Again $2n - (2n-1) = 1$,

$$\begin{aligned}
\sum_{n=0}^{p-1} \left(\frac{p-n}{p} \right)^3 (-1)^n &= \frac{1}{p^3} \sum_{n=0}^{\frac{p}{2}} 1 \times ((2n)^2 + 2n(2n-1) + (2n-1)^2) \\
&= \frac{1}{p^3} \sum_{n=0}^{\frac{p}{2}} (12n^2 + \text{terms of power 1 or less}) \\
&= \frac{12}{p^3} \left(\frac{(p/2)^3}{3} + \text{terms of power 2 or less} \right) \\
&= \frac{1}{2} + \left(\text{terms that are functions of } \frac{1}{p} \right)
\end{aligned}$$

Since all terms with p as a denominator term go to zero as $p \rightarrow \infty$, we find that,

$$\sum_{n=0}^{p-1} \left(\frac{p-n}{p} \right)^3 (-1)^n \rightarrow \frac{1}{2} \text{ as } p \rightarrow \infty$$

2.4 Analytical Solution for $i \in \mathbb{Z}$

$$\sum_{n=0}^{p-1} \left(\frac{p-n}{p} \right)^i (-1)^n = \frac{1}{p^i} [p^i - (p-1)^i + (p-2)^i - (p-3)^i + \dots] \quad (4)$$

As before, group in pairs, denoted as $2n$ and $2n-1$ where $n = 1, 2, 3, \dots, p/2$. Since $x^i - y^i = (x-y)(x^{i-1} + x^{i-2}y + \dots + y^i)$, we can write,

$$\sum_{n=0}^{p-1} \left(\frac{p-n}{p} \right)^i (-1)^n = \frac{1}{p^i} \sum_{n=0}^{\frac{p}{2}} (2n - (2n-1)) \times ((2n)^{i-1} + 2n^{i-2}(2n-1) + \dots + (2n-1)^{i-1})$$

Again, $2n - (2n-1) = 1$, so,

$$\begin{aligned}
\sum_{n=0}^{p-1} \left(\frac{p-n}{p} \right)^i (-1)^n &= \frac{1}{p^i} \sum_{n=1}^{\frac{p}{2}} 1 \times (i(2n))^{i-1} + \text{terms of power } i-2 \text{ or less} \\
&= \frac{1}{p^i} \sum_{n=1}^{\frac{p}{2}} (i(2^{i-1})n^{i-1} + \text{terms of power } i-2 \text{ or less}) \\
&= \frac{1}{p^i} i 2^{i-1} \sum_{n=1}^{\frac{p}{2}} ((n^{i-1}) + \text{terms of power } i-2 \text{ or less})
\end{aligned}$$

Using the identity

$$\sum_{k=1}^n k^\Gamma = \frac{n^{\Gamma+1}}{\Gamma+1} + \text{terms of power } < \Gamma + 1$$

we can write,

$$\begin{aligned}
\sum_{n=0}^{p-1} \left(\frac{p-n}{p} \right)^i (-1)^n &= \frac{1}{p^i} i 2^{i-1} \left(\frac{(p/2)^i}{i} + \text{terms of power } i-1 \text{ or less} \right) \\
&= \frac{1}{p^i} i 2^{i-1} \left(\frac{p^i}{i 2^i} + \text{terms of power } i-1 \text{ or less} \right) \\
&= \frac{1}{2} + \left(\text{terms that are functions of } \frac{1}{p} \right)
\end{aligned}$$

Since all terms with p as a denominator term go to zero as $p \rightarrow \infty$, we find that,

$$\sum_{n=0}^{p-1} \left(\frac{p-n}{p} \right)^i (-1)^n \rightarrow \frac{1}{2} \text{ as } p \rightarrow \infty$$

The solution, for each case presented, hinges on the fact that $(x-y)$ is always a factor of $x^i - y^i$.

3 Lorenz Curves and a Tentative Solution

Wealth distribution in society is characterised by *concentration indicators*, i.e. things that help illustrate how wealth is concentrated, e.g. salaries. By observing how the value, or concentration, of salary payments varies among the population, some understanding of inequality, or otherwise, within the society is established [2].

In general, Lorenz curves take the form of a cumulative normalised wealth measure on the y -axis and a cumulative normalised population measure on the x -axis. The scale, then, varies from zero to one, or 0% to 100%, on both axes [6].

It is perhaps not much of a leap to see that the generalised Pohlhausen solution, which describes the drug dissolution rate from the surface of a tablet as a function of the number of layers of drug, is an equivalent idea: the *cumulative normalised drug dissolution rate* is used in place of *cumulative normalised wealth* and *normalised layer number*, e.g. layer two of five (2/5), is equivalent to the *cumulative normalised population*.

The quantity $\left(\frac{p-n}{p}\right)^i$, from Equation 3, can be mapped onto an expression for the cumulative frequency distribution of a Pareto distribution, a type of Lorenz curve. Equation 3, however, differs from the description of a Lorenz curve in one important way: the factor $(-1)^i$ means that every other term is negative. As the number of layers grows large, the number of subtractions approaches half the total number of layers. Since the cumulative normalised wealth in a Lorenz distribution must equal 100% overall, it follows that Equation 3 will approach 0.5 (or 50%) as the number of layers grows large, i.e. we subtract out approximately half the terms, i.e.

$$\sum_{n=0}^{p-1} \left(\frac{p-n}{p}\right)^i (-1)^n \rightarrow 0.5 \quad (5)$$

for all $i > 0$ as p becomes large. So, as p becomes large, and with the results from earlier in this note, we can write that,

$$\frac{\dot{m}_{\text{excipient}, p \text{ layers}}}{\dot{m}_{\text{excipient}, 1 \text{ layer}}} \approx \left[\frac{1}{2} \right]^{\frac{2}{3}} = 0.63 \quad (6)$$

$$\frac{\dot{m}_{\text{drug}, p \text{ layers}}}{\dot{m}_{\text{drug}, 1 \text{ layer}}} \approx \left[\frac{1}{2} \right]^{\frac{2}{3}} = 0.63 \quad (7)$$

4 Conclusion

It was interesting to find that the generalised Pohlhausen solution [3] is effectively a modified Lorenz curve. It's not so surprising in retrospect: the problem of drug dissolution rate from a multi-layer tablet in a steady flow is, in abstract, the same as wealth and population. Instead of wealth and population, we have drug dissolution rate and number of layers. Just as a nation's wealth is a fixed value, the overall dissolution rate from a dissolving compact is a single value. As each citizen contributes some of the nation's wealth, each layer contributes to some of the tablet's overall dissolution rate. Finally, for the system considered, this fixed value is 63% of the drug dissolution rate for a compact that consists entirely of drug.

References

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- [6] S. VARONE, *Measure of Concentration (Notes)*. Online, 2012.

Appendix

```
#This Python script (http://www.python.org/) sums the general series
#described in this technical note.
```

```
#Date: 11/2012.
```

```
#Copyright (C) 2012 Niall McMahon (nmcMahon@computing.dcu.ie)
```

```
#See: http://niallmcmahon.com/legals.html
```

```
print
```

```
print "Copyright (C) 2012 Niall McMahon. This code comes with ABSOLUTELY NO WARRANTY."
```

```
print
```

```
#m is the upper limit and i is the index.
```

```
m = 5
```

```
i = 0.25
```

```
sum = 0.0
```

```
n = 0.0
```

```
while n < m:
```

```
    x1 = pow((m-n)/m,i)
```

```
    x2 = pow(-1,n)
```

```
    nextterm = x1*x2
```

```
    sum = sum + nextterm
```

```
    n = n + 1
```

```
#Prints the sum
```

```
print "Sum for m =",m," i = ",i,":",sum  
print
```

Acknowledgements

The authors would like to thank Professor Martin Clynes and the Irish National Institute for Cellular Biotechnology (NICB) for its support. Additional support from the Institute for Numerical Computation and Analysis (INCA) was invaluable. Prof. Michael Ryan of the School of Computing at DCU provided useful suggestions about how to proceed with this problem. Sandra Spillane of Dublin Institute of Technology provided useful help. Susan Lazarus and Aongus Ó Cairbre at Dublin Institute of Technology advanced the solution for exponents of positive integers, as outlined in this document. Deirdre D'Arcy of the School of Pharmacy and Pharmaceutical Sciences at Trinity College Dublin provided useful experimental observations, as always.