Calculations on the feasibility of the DrugPrinter

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This is a series of calculations to demonstrate the infeasibility of the *DrugPrinter* reported in *Drug Discovery Today.*[1] They are also applicable to any methodology where molecules are built one at a time. A commenter (YC) claiming to be the author has posted some of the referee's comments and his replies online.[2] I've responded to one of them there but YC doesn't understand/believe me so this is a long form version. Quoted text are taken from YC's comments, I've not reproduced the full text but they are available at the link below.

> 3) I still think that you need to give some estimates of the following: a. How long would it take to make a single compound of (for example) 350Da
>
> ...From the aforementioned video, we know made a compound maybe only need less than 1 Nano second. However, if we want to make 1 pmole of this compound. For example, 1 pmole of a 350 molecular weight de novo compound need 350 g x 10^-12. I estimate roughly (6x10^23) x (10^ -12)x (10^-9)/60sx60min=1.66 pmole/min...

My initial response made use of dimensional analysis to try and work out what this equation means. I assumed the 10^{-9} came from the aforementioned nanoseconds.

$$\frac{6 \times 10^{23} \times 10^{-12} \times 10^{-9}}{60 \times 60} = 1.66 \text{ pmol/min} \tag{1}$$

$$\frac{\text{mol}^{-1} \times \text{mol} \times \text{s}}{\text{s} \times \text{min}} = \text{min}^{-1} \tag{2}$$

If you multiply out the left hand side of equation 1 you end up with 0.166 not 1.66. From the dimensional analysis we get units of min^{-1} (i.e. a frequency) as Avagadro's constant has units of mol^{-1}, but here we are refering to molecules per mole so this becomes molecules/min. A rate of 0.166 molecules/min is ridiculously slow sp thankfully it's wrong.

Instead, returning to your initial numbers you gave a time of 1 ns (10^-9 s) to synthesise 1 molecule. Therefore we can calculate how long it takes to make 1 pmole (10^{-12} moles) of a compound.

$$\begin{aligned} \text{No. of molecules} &= N_A \times \text{moles} && (3)\\ &= 6.022 \times 10^{23} \times 10^{-12} && (4)\\ &= 6.022 \times 10^{11} \text{ molecules} && (5)\\ \text{Time to 1 pmol} &= \text{No. of molecules} \times \text{Time to synthesise 1 molecule} && (6)\\ &= 6.022 \times 10^{11} \times 10^{-9} && (7)\\ &= 602.2 \text{ s} \simeq 10 \text{ minutes} && (8) \end{aligned}$$

Thus your rate of synthesis is approximately 0.1 pmol/min not the 1.66 you quoted.

> ...and i had mention in the manuscript, this tech is not for fabricate large amount compound. it only design for us (CADD) to test the bioassay.

I appreciate that the aim isn't to produce a large amount of compound but as I mentioned in my previous reply 1 pmol of a compound is a vanishingly small quantity of material. For the aforementioned theoretical 350 Da drug candidate that's 350 pg. I've personally performed assays at pM or even fM concentrations but there are several caveats that allowed this:

1. the materials were macromolecules or viruses (molar masses 10^5–10^8 Da) and so a small molar quantity is comparitively larger mass.
2. there are well-established measurements for these materials that don't require weighing
3. if an alternative method of determining quantity wasn't available I had enough material to weigh accurately (10s of mg) then perform serial dilutions to the required concentration

For your *de novo* compounds the first two aren't available and so that last one is required if you are to get any meaningful data. In my previous reply I stated that a microgram would be the minimum but that is still impossible to weigh accurately and will not allow any thorough characterisation of the what is supposed to be a novel material. If these leads are to be translated to pre-clinical measurements then you need to be sure that it's what you think it is before making enough to be useful. Consequently I'm going to repeat the calculations using 1 milligram as minimum quantity required for characterisation (^{1}H and ^{13}C NMR, mass spec and HPLC) and biological analysis. For the calculations I'll be using the following numbers.

$$\text{Rate of Synthesis} = 0.1 \text{ pmol/min} = 10^{-13} \text{ mol/min} \tag{9}$$
$$\text{Molar Mass of Target} = 350 \text{ g/mol} \tag{10}$$
$$\text{Required Mass of Target} = 1 \text{ mg} = 10^{-3} \text{ g} \tag{11}$$
$$\tag{12}$$

We can then calculate the time required to make 1 mg as follows.

$$\text{Required Moles of Target} = \frac{\text{Required Mass of Target}}{\text{Molar Mass of Target}} = \frac{10^{-3}}{350} = 2.86 \times 10^{-6} \text{ mol} \tag{13}$$
$$\text{Time to Print Required Moles} = \frac{\text{Required Moles of Target}}{\text{Rate of Synthesis}} = \frac{2.86 \times 10^{-6}}{10^{-13}} = 2.85 \times 10^{7} \text{ min} \tag{14}$$

Converting this to other units of time

$$\text{Time in hours} = \frac{2.86 \times 10^{7}}{60} = 4.76 \times 10^{5} \text{ h} \tag{15}$$
$$\text{Time in days} = \frac{4.76 \times 10^{5}}{24} = 1.98 \times 10^{4} \text{ days} \simeq 20000 \text{ days} \tag{16}$$
$$\tag{17}$$

You'll notice this is ∼1000 times larger than before as I'm now looking for 1 mg rather than 1 μg. I previously said 57 years to a mg. Using a calculator rather than a rough estimate in my head we get:

$$\text{Time in Years} = \frac{1.98 \times 10^{4}}{365} = 54\text{years} \tag{18}$$

The next part of my comment related to your reply to the referee.

> If we use many set of these tiny reactor in the same time. It can reach Mass Production kilogram of product per minute. So I dont think the difficulty is the speed of production but in how to separate the product from the tiny mode.

If it takes 2.85×10^7 minutes to make 1 mg of product then we can calculate the time to a kg

$$\text{Time to 1 kg} = 10^6 \times \text{Time to 1 mg} = 2.85 \times 10^7 \times 10^6 = 2.85 \times 10^{13} \text{ min} \tag{19}$$

Thus the rate of synthesis in kg/min can be calculated

$$\text{Rate in kg/min} = \frac{1}{\text{Time to 1 kg}} = \frac{1}{2.85 \times 10^{13}} = 3.5 \times 10^{-14} \text{ kg/min} \tag{20}$$

We can then calculate the number of printers to reach the desired rate of 1 kg/min.

$$\text{No. of Printers} = \frac{\text{Desired Rate}}{\text{Rate of 1 Printer}} = \frac{1}{3.5 \times 10^{-14}} = 2.85 \times 10^{13} \tag{21}$$

Unsurprisingly this is the same number as the amount of minutes it takes 1 printer to make a kg.

The final part of my comment referred to the amount of space required to house this many printers. I took a very optimistically small volume for each printer of 1 cm^3 (i.e. 1 mL).

$$\text{Volume of printers} = 2.85 \times 10^{13} \text{ mL} \tag{22}$$

$$= 2.85 \times 10^{10} \text{ L} \tag{23}$$

I then chose a slightly facetious comparison as to a similar volume, that of annual, international crude oil shipping. Here, instead, I'll use the volume of one of the largest oil tankers around.[3] This has a capacity of $\sim 5 \times 10^8$ L, you'll need approximately 57 of them to house your printers to reach this synthesis rate.

References

[1] C. Y.-C. Chen, *Drug Discovery Today* **2014**, DOI: 10.1016/j.drudis.2014.03.027.

[2] http://quintus.mickel.ch/2014/04/19/print-your-own/#comment-151625.

[3] http://en.wikipedia.org/wiki/TI_class_supertanker.