

## < Dallphin-AtoM ver. 0.8.5 Brief users' guide>

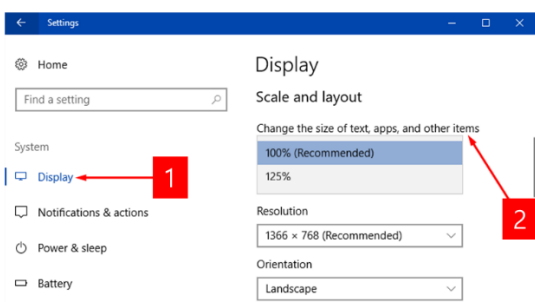
If you are using a laptop or an internal or external monitor with Ultra High Definition (4k UHD) using a higher resolution, you might experience the following problems in Dall-Phin.

- Elements are too small or large compared to the rest of the desktop.
- Elements such as icons, toolbars, text, and dialog boxes appear to be fuzzy or disoriented.
- Blurry text appears in Dall-Phin interface.

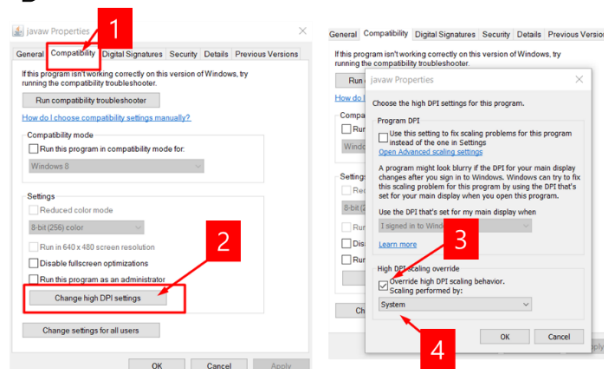
You can solve these problems by applying one of the following solutions.

1. Change the size of apps: You can right-click on the Desktop (background image) > Display Setting > Change the size of apps, text, and other items on the screen. (100%) (Figure 1A)
2. Change the Java compatibility properties of Javaw.exe: You can find javaw.exe in C:\WDALL-Phin\Wjrewhbin in the Explorer and follow these actions: Right click > Properties> Compatibility tab > Change high dpi settings > Click override system settings. (Figure 1B)

A



B



## What is Dallphin-AtoM?

- Dallphin is the acronym of the phrase '**D**rugs with **ALL**ometry and **PH**ysiology **I**Nside' and AtoM is '**A**nimal to hu**M**an'.
- It is a PBPK software that predicts human PK parameters and plasma drug concentrations based on many published methods using physicochemical properties, in vitro and animal PK data.

## Why Dallphin-AtoM?

- There are several commercial and free PBPK software packages already available for human PK prediction.
- However, we felt needs for something that does not request overly many parameters and that clarifies all of the methods and/or references used to predict human PK to the researchers using the software.
- Also, less restriction in the accessibility, right to use, or affordability for both of the academia and industry was what we've sought for.

### **Right to use Dallphin-AtoM**

- Dallphin-AtoM (Dallphin, for simplicity) 0.8.5 is distributed to beta testers for test use only.
- Any suggestion, comments or bug reports via email ([yimds@catholic.ac.kr](mailto:yimds@catholic.ac.kr)) are welcomed.

### **Who developed Dallphin-AtoM?**

- Dallphin 0.8.5 was developed by researchers of PIPET (Pharmacometrics Institute for Practical Education and Training) of College of Medicine, the Catholic University of Korea for the education of students and researchers.
- Dallphin 0.8.5 was developed as a part of the EDISON (EDucation-research Integration through Simulation On the Net) Program of the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (grant number: 2016M3C1A6936614).

### **Disclaimer**

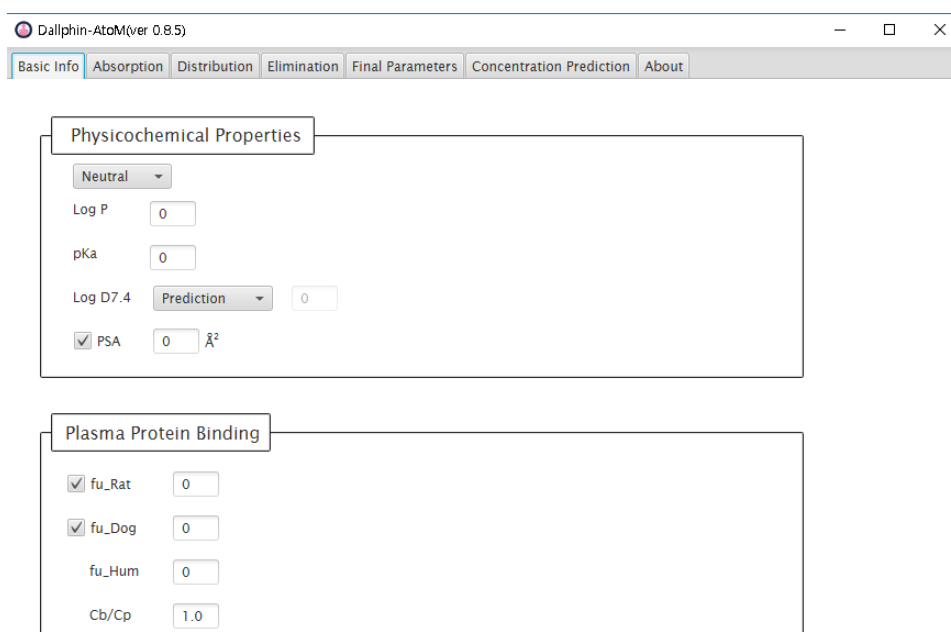
- All of the predictions by Dallphin are calculated based on equations published in research articles (peer reviewed journals) and textbooks on PK, PBPK and allometry. The accuracy, adequacy, validity, reliability, or completeness of any information provided by Dallphin is dependent on the references that were used in Dallphin. Under no circumstances shall the developers of Dallphin have any liability to the users for any loss or damage of any kind incurred as a result of the use of Dallphin or reliance on any information provided by Dallphin.
- The user may not modify contents of the Dallphin, nor distribute the modified installation files.

## What this guide tells

- To predict drug exposure in human, we need to know four major PK parameters -  $K_a$ ,  $V_d$  ( $V_c$ ,  $V_p$  and  $Q$ ),  $CL$  and  $F$  if the drug follows first-order kinetics.
- This guide introduces the principles used in the prediction of each of the 4 PK parameters based on in vitro or animal PK data together with corresponding references. (Demonstrating how to use Dallphin is not the purpose of this guide: it will be open as a video file in the web.)
- You may find more detailed introduction to the theories and equations used in Dallphin in two lecture slides (pdf documents) that may be downloaded by clicking on the "About" tab of Dallphin.

## Brief Introduction of the tabs

- When Dallphin is launched in your computer, you'll see six tabs. From the leftmost one, you should enter your own laboratory results requested in each tabpane.
- When the entering job is done from the 'Basic info' to the 'Elimination' tab, you may click the 'Final Parameters' tab to see all of the predicted human PK parameters.
- Lastly, you will observe the predicted plasma concentrations at the "Concentration Prediction" tabpane.



Dallphin-AtoM(ver 0.8.5)

Basic Info | Absorption | Distribution | Elimination | Final Parameters | Concentration Prediction | About

**Physicochemical Properties**

Neutral

Log P

pKa

Log D7.4

☒ PSA  Å<sup>2</sup>

**Plasma Protein Binding**

☒ fu\_Rat

☒ fu\_Dog

fu\_Hum

Cb/Cp

## Basic info Tab

- In the Basic info tabpane, physicochemical properties, blood-to-plasma concentration ratio and plasma protein binding are input.
- Log D may be directly input by the user or calculated from log P and pKa values.
- The physicochemical property inputs are used at the calculation of unbound fraction in the microsome or hepatocytes at the 'Elimination' tab. The unbound fraction is then used to predict hepatic CL, although it does not appear as final parameters.
- When PSA (polar surface area) value is input, Fa calculated using PSA [1] is shown at the Absorption tabpane as Fa\_PSA.

## Absorption Tab

### **<Caco-2 permeability and Fa>**

- Caco-2 permeability of the drug should be input as Papp. Those from reference standard drugs (atenolol and/or verapamil) are also recommended to input if available.
- The Peff (permeability in human duodenum) is calculated from the Papp (or corrected Papp if Papp of reference drugs are available) which is in vitro data [2].
- Caco-2 cell based Fa (fraction absorbed,  $F = Fa \times F_{gut} \times F_H$ ) was then calculated using equations on the relationship between Fa, Peff, small intestine surface area and its transit time [3].
- MDCK-II cell permeability can be input or predicted using Caco-2 Papp to estimate passive CL that may be used when microsomal method is chosen for the calculation of hepatic CL.
- The Fa calculated herein is given as Fa\_Caco in the bottom of the pane.

### **<MDCK permeability>**

MDCK-II cell permeability may be input here when available.

### **<first-order absorption rate constant: ka>**

- We used an equation [4] to predict human ka that is calculated from Caco-2 permeability data, intestinal surface area and Vc (central compartment Vd).

- In a one compartment model, to predict the  $k_a$  value, we assume the  $V_d$  as  $V_c$ . This may cause some discrepancy in  $k_a$  prediction, we highly recommend you to use two compartment model.

\*The first-order oral absorption model has been criticized as physiologically unreliable and sophisticated models such as ADAM or ACAT have been proposed. However, to use those models properly, the user should input detailed information on the metabolic pathways and metabolic ratios of the molecule, which is not commonly practiced in preclinical development phases unless the company has an internal policy of intense metabolic profiling before clinical development. Thus, Dallphin employed the old, conventional parameter  $k_a$ , assuming first-order absorption for simplicity. (Though this may not be sophisticated, seems cost-effective in preclinical to clinical prediction.)

### **Distribution tab**

- Both of the allometric method (proportional to body weight) using animal PK data and the PBPK model-based method using physicochemical properties and physiological values are available to predict human  $V_d$  in Dallphin-AtoM. The user should opt for one in the two.

#### **<Allometric method>**

- Compartmental PK parameters on distribution ( $V_c$ ,  $V_p$  and  $Q$ ) obtained from i.v. PK study in more than two animal species (mouse, rat, dog, monkey) is a necessity to use the allometric method.
- The user may choose either one- or two-compartment models, and the number of compartments should be same for all of the animal species used. (The number of distribution compartments  $\geq 3$  is not acceptable.)
- In case of two compartment model:
  - $V_c$  and  $V_p$  in each species are to be input by users and  $V_{ss}$  is automatically filled up ( $V_{ss} = V_p + V_c$ ).
  - Dallphin calculates human  $V_{ss}$  and  $V_c$  allometrically with the exponent to body weight fixed to 1.
  - Although there is no report on the allometric estimation of  $V_c$ , we assumed that both of  $V_c$  and  $V_{ss}$  are proportional to body weights regardless of species.
- In case of one compartment model:

- The user may also opt for "1-compartment" model instead of "2-compartment model". Occasionally, the i.v. PK data may be better fitted by a 1-compartment model according to the PK sampling scheme, infusion time, or else. Even when the i.v. PK profiles in animals seem to follow multi-compartment models, software for compartmental analysis may not be available to the user. Then, the user may input Vss obtained from non-compartmental analysis in the "1-compartment" model.
- Vp or Q are not requested.

#### **<PBPK method>**

- If animal PK data is not available, Vss is predicted from the PBPK-based prediction method which uses drug lipophilicity, organ fat content and other tissue physiologic factors [5-7]. All of the physiological variables from the references are used in Dallphin AtOM as built-in equations to calculate Vss. When using the PBPK method, only Vss is calculated (without presenting Vc and Vp separately) as if the drug follows a 1-compartment model.

### **Elimination tab**

#### **Hepatic CL**

- For hepatic CL, the user should opt for either of microsome or hepatocyte based on the user's experimental data (done with microsome or human hepatocyte).
  - The well-stirred model equation which defines the relationship of hepatic blood flow, hepatic intrinsic CL, plasma unbound fraction and blood-to-plasma concentration ratio was used to calculate various hepatic CLs from microsomal or hepatocyte experimental data.

#### **<microsome experiment data>**

- The microsome protein concentration can be input considering the user's experimental condition.
- In the microsome experiment, when the user inputs microsome intrinsic CL (CL int\_ini), it is corrected by nonspecific binding fraction predicted by 'logD' or 'logP' value [7] and scaled up by the amount of protein per gram liver and weight of liver to predict the human hepatic CL (CLh).
- As intrinsic CL can be over-predicted in microsome experiments, passive diffusion CL may be applied on intrinsic metabolic CL to reflect the diffusion rate of drug molecules across

the hepatocyte cell membrane. The user can select whether the CL<sub>h</sub> is corrected by passive diffusion CL (to obtain CL<sub>PS</sub>) or just use the CL<sub>h</sub> as is.

- Passive diffusion CL was calculated using either the apparent passive permeability (P<sub>app</sub>) of MDCK-II cell and surface area of one million human hepatocytes. However, in case the MDCK-II cell P<sub>app</sub> is not available, the user may use P<sub>app</sub> of Caco-2 cell permeability or logD to predict the MDCK-II cell P<sub>app</sub> value. [8]. The corrected CL<sub>h</sub> obtained using MDCK-II or Caco-2 P<sub>app</sub> is CL<sub>h,PS</sub>. When the CL<sub>h</sub> is corrected with logD instead of MDCK-II or Caco-2 permeability data, it is named CL<sub>h,PS(logD)</sub>.
- Correction using rat in vitro-in vivo correlation (ivivc) data:
  - When both of rat microsomal experiment data (CL<sub>int,ini</sub> of the rat) and rat *in vivo* hepatic CL (CL<sub>h,ratinvivo</sub>) are available, their ratio may be applied to obtain corrected human hepatic CL.
  - First, corrected CL<sub>int,ini</sub> of rat (CL<sub>int,ini'</sub>) is back-calculated from observed CL<sub>h</sub> of rat (CL<sub>h,ratinvivo</sub>)
  - Second, the ratio between the CL<sub>int,ini</sub> and its corrected value in rat is calculated.
  - Third the ratio is used to correct the CL<sub>int,ini</sub> of human.
  - Last, the human corrected CL<sub>int,ini</sub> is used to calculate CL<sub>h,fromrativivc</sub> using the well-stirred model equation.
- Correction using rat ivivc is not provided for CL<sub>h,PS</sub> or CL<sub>h,PS(logD)</sub> because experiments on rat hepatocyte permeability is not generally done.

**<When using hepatocyte experiment data>**

- The hepatocyte cell volume ratio can be input considering the user's experimental condition. Generally, it is considered to be 0.005 when 10<sup>6</sup> hepatocyte cells were used.
- In this case, when the user inputs intrinsic CL of hepatocyte, it is corrected by nonspecific binding fraction predicted by 'logP' or 'logP' value [7] and scaled up by the number of hepatocytes per gram liver and weight of liver to predict the intrinsic metabolic CL.
- The well-stirred model equation which defines the relationship of hepatic blood flow, hepatic intrinsic CL, plasma unbound fraction and blood-to-plasma concentration ratio was used to calculate the hepatic CL.

- The ivivc correction using rat data as in the case of microsomal experiment is not provided because in vitro metabolism study using rat hepatocytes is not frequently performed.

### **Renal CL**

- Renal CL of human is predicted directly from the rat or dog renal CL corrected by fraction unbound in plasma and kidney blood flow of each animal. [9]
- If an assumed human renal CL value of the new molecule is available (from information on the same category drugs or else), the user may directly input the value in the Final parameters tabpane.
- The user can select one of the renal CL predicted from animals or directly input by the user (assumed human renal CL) for calculating total CL in human in the Final parameters tabpane..

### **Final Parameters tab**

- The user may choose preferred hepatic CL, Fh, renal CL and Fa values for simulation among several differently calculated parameters in the previous tabpanes.
- Since Fh value is derived from hepatic CL, Fh and hepatic CL is paired and the Fh value will be automatically selected when the hepatic CL is selected.
- The user has four pairs of choices in hepatic CL and Fh when using microsome intrinsic CL, and the user has one pair of choice in hepatic CL and Fh when using hepatocyte intrinsic CL.
- The user may select one of the two renal CL (from rats or dogs) or enter the assumed renal CL value for simulation.

### **Concentration Prediction tab**

- Human plasma concentration-time curves after oral or i.v. dosing are simulated using the dose, interval, number of doses input by the user and the final human PK parameters. If necessary, population PK distribution may also be simulated. Results and input parameters are also saved in the result folder ('Open Result Folder').



## References

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